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An operating room with high atmospheric pressure

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In 1956 the results of a series of experiments concerned with heart surgery and carried out in a caisson were published. These experiments were performed in a closed steel room in which the atmospheric pressure was brought up to 3 atmospheres (absolute). The operating staff inside the room worked under these high-pressure conditions. The results of the experiments were striking.

Since 1841, when Tiger of France developed the caisson as an aid to the underwater works necessary for building pillars for bridges and similar projects, much work has been done by men under high pressure, even up to 4 or 5 atmospheres (absolute). While experience was being gained, many dangers were encountered. However, the only real danger was "caisson disease," the cause of which was eventually recognized as being a too rapid return from high pressure to normal atmospheric pressure. Neither the compression itself nor working under hyperpression proved a danger and even heavy work was more easily performed in the caisson. The only danger was leaving the tank. As Pol and Watelle clearly expressed, "On ne paye qu'en sortant." However, once the cause of caisson disease was clearly understood and after Haldane had laid down strict rules for the decompression time, it could be stated that work can be carried on in a hyperpression tank without any danger, provided that the hyperpression is not too high—not over 3 atmospheres (absolute), and provided that persons subjected to hyperpression are free from head colds or dental abscesses. A healthy man can work many hours a day under a pressure of 3 atmospheres (absolute), breathing air. No signs of oxygen intoxication or nitrogen narcosis need be feared. However, when the person is breathing pure oxygen, the time is limited. According to Behnke,[2] breathing pure oxygen at 3 atmospheres pressure for more than 3 hours is deleterious to the lungs and central nervous system. Within these limits, however, there is no risk involved. My assistants and I have worked over 100 times in the hyperpression tank. None of us, or the animals, or the patients suffered any harm. We thus feel quite safe when working inside the apparatus.

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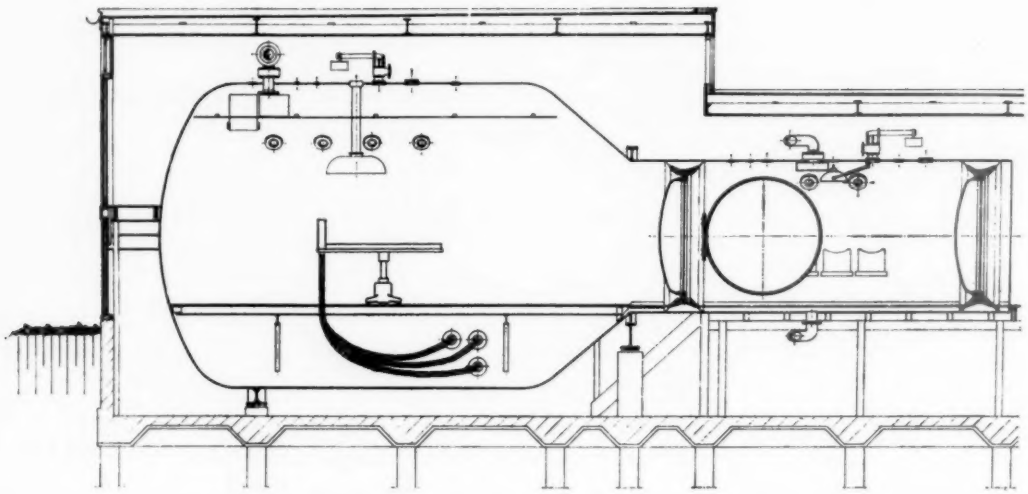

Fig. 1. Longitudinal section through the high-pressure operating room.

For more than a century the influence of hyperpressure on men and animals has been studied. Publications appeared of the many observations made at various places. In 1878 Bert[3] gathered together in a splendid book all the scattered knowledge, added accounts of a large number of important experiments carried out in his laboratory, and pointed out new possibilities for the future. Until that year therapeutic hyperpressure had been used only on a small scale. In many of the large cities in Europe 100 years ago, a caisson was available for patients, who, sitting inside for a few hours, breathed air at ¼ to ⅓ atmospheric hyperpressure. Good results were expected in various diseases. Since by the end of the last century these hyperpressure chambers had practically disappeared, it may be concluded that the results in the long run were not very convincing.

In 1879, Fontaine, using an overpressure of ⅓ to ¼ atmosphere, tried to improve nitrous oxide anesthesia by use of these tanks. The nitrous oxide gas, being more soluble under hyperpressure, gave a better, easier, and more comfortable narcosis. Nearly 30 patients were anesthetized in this way and the results were recorded as being very satisfactory. Fontaine contemplated building a real operating theater, large enough to contain a complete operating staff. However, it was never built.

Bloodless operation under low hyperpression was first performed by Pravaz in 1843. He advised treating dislocated hips in a hyperpressure room. Bert advised raising the overpressure to 3 atmospheres, pointing out that the reduction of an incarcerated hernia should be tried in these caissons, for the gases in the bowel would be compressed to a much smaller volume and in this way reduction would be facilitated.

In our time, Lovelace (quoted by Wangensteen[25]) anticipated that patients with ileus treated in a hyperpression tank would improve. The gases in the bowel would diffuse more easily through the epithelium into the blood. Wangensteen[26] has tried this in a very small caisson in his department.

As far as we know, true operative surgery has never been performed in a hyperpression tank before our experiments in 1956. Ordinary operative techniques have been carried out with the whole operating staff, consisting of surgeons, anesthetists, and orderlies, inside the closed caisson with the air pressure at 3 atmospheres (absolute). The results were so promising that, after having worked for some years in a small tank at the Royal Dutch Navy School, we decided to build a

large tank on the grounds of the Wilhelmina Hospital of the University of Amsterdam, close to the surgical department. The tank was large enough to serve as an operating theater. It was completed in 1959 and after some small problems had been overcome, it was ready to accomodate operations under high pressure. It is now in use nearly every day, either for operations or for nonoperative treatment of surgical patients.

Since this is the first high-pressure operating room in the world, it merits a short description.

The operating theater is a large cylindrical steel room, closed off at both ends by hemispherical steel plates. In one of the latter is a large steel door, which can be closed hermetically. The floor surface is a little over 4 by 6 meters. The ceiling is of a special construction in order to eliminate the annoying noise produced when the compressed air is blown in. Everything in the tank, the walls, the ceiling, and the stools, is of metal. The paint on the walls is of a noninflammable nature. Small glass windows are situated on both sides of the tank, primarily to enable the controlling engineer to view the scene inside and also to allow the students and visitors to follow the operation from outside. Inside the tank above the operating table is a microtelephone by means of which the staff inside and the engineers outside are able to communicate. A small lock allows surgical instruments, drugs, hot or cold water, and so forth, to be taken in or out of the tank during the operation.

A large lock situated in front of the main room enables the latter to be left or entered without disturbing the operation in progress. This lock is sufficiently large to be used for operations and experiments on small animals.

A pressure of 3 atmospheres (absolute) can be achieved in approximately 12 minutes. This quick compression causes a

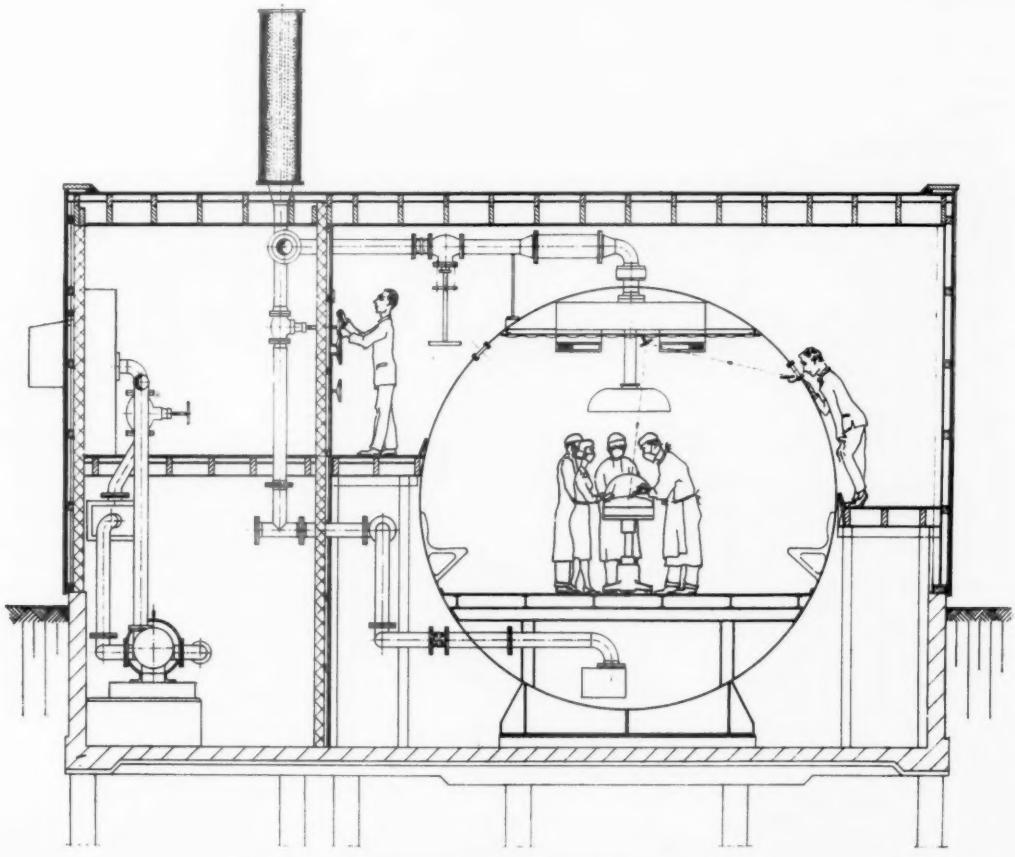

Fig. 2. Transverse section of the operating room.

Fig. 3. The high-pressure chamber placed on its foundations. A building was constructed around it afterward.

sharp rise in the air temperature and necessitates a complicated cooling system. Solving the problems associated with the regulation of the cooling of the compressed air, of illumination, and of the noise caused by the insufflation of fresh air, necessitated close cooperation of many specialists in the fields of engineering and of physics. Everything had to be calculated exactly before construction could be started, particularly since once the tank had been placed on its foundation, it was forbidden by law to change anything within the body.

Nearly half of the assistants on the staff of the surgical and anesthesiological departments were able to work in the high-pressure theater. The other half complained of pain in the ears or sinuses as soon as the pressure rose to more than 4 or 5 meters of water. Those who were able to work in the tank experienced no difficulties whatsoever, either physical or mental. Patients treated in the pressure room and who were conscious had no feeling of claustrophobia and were very willing to re-enter the high-pressure chamber several times if necessary.

RESEARCH PROJECTS

The program of the surgical and medical work in the high-pressure room up to the present consisted of research on 4 subjects. Two of the problems have been solved since 1956.

The research projects are all based on the common principle that when an animal or patient breaths pure oxygen at 3 atmospheres (absolute) there is a greatly increased physical solution of oxygen in all tissues of the body, both fluid and semifluid.

We were interested mostly in this method as an aid to open-heart surgery, but it soon proved to be of value in other surgical fields.

Project 1. First we proved that when the venae cavae are clamped, the blood circulation can be arrested for about twice as long as is possible at normal atmospheric pressure with a moderate hypothermia of 29° C. The explanation of this phenomenon is to be found in the extreme saturation of the whole body with physically dissolved oxygen, so that the cells have a much higher reserve of oxygen than they normally have. Hill showed that a physical increase in the amount of oxygen in the tissues did not raise the chemical uptake of oxygen in hemoglobin. We may assume, then, that the increased amount of oxygen in solution provides a true reserve for the tissues and, consequently, that the tissue cells can withstand a circulatory arrest of longer duration.

Project 2. Gesell, Lambertsen, and several other authors calculated that the amount of physically dissolved oxygen in a patient breathing oxygen at 3 atmospheres was about the same as is normally delivered to the tissues by the oxyhemoglobin in the red cells. Consequently, under these conditions, oxyhemoglobin could be bypassed completely as a means of transporting oxygen.

We diluted the blood of small pigs with a clear fluid, either plasma or macrodex, to

reduce the percentage of oxyhemoglobin of the blood. While they breathed oxygen at normal pressure the hemoglobin could be reduced to a level of 11 or 12 per cent before the electrocardiogram showed any signs of anoxia of the heart muscle. At an oxygen pressure of 3 atmospheres (absolute), however, the hemoglobin could be lowered to 0.4 per cent, that is, to practically zero, without the myocardium showing any signs of anoxia on the electrocardiogram. The animal breathed spontaneously and maintained a normal blood pressure. There was a constant fall in pH but mostly of an insignificant degree. A quarter of an hour later reinfusion of blood was started, so that at the end of the experiment the animal had acquired the same level of oxyhemoglobin in the blood as before. The reawakening was rather slow, but soon the animals behaved normally and showed no late complications during the following weeks. Apparently no harm was done to the tissues, particularly those of the heart, liver, or brain. The amount of oxygen available in physical solution proved to be completely adequate under these conditions. The circulating "blood" was an almost clear, transparent fluid.

Project 3. From the literature it is not quite clear whether the irritability of the heart in a state of hypothermia at about 26° to 20° C., which very often leads to fibrillation when the heart is surgically touched, is a consequence of lack of oxygen or not. The results of experiments by different workers in this respect concerning the significance of the quantity of oxygen available are opposing. The oxygen in these experiments is carried mainly by the oxyhemoglobin and it is questionable whether this oxygen can be utilized by the tissues under hypothermia at normal atmospheric pressure.

However, when an animal or patient breathes pure oxygen at 3 atmospheres absolute pressure, an enormously increased amount of physically dissolved oxygen is present, not only in the blood, but in all tissues. It might therefore be possible to cool

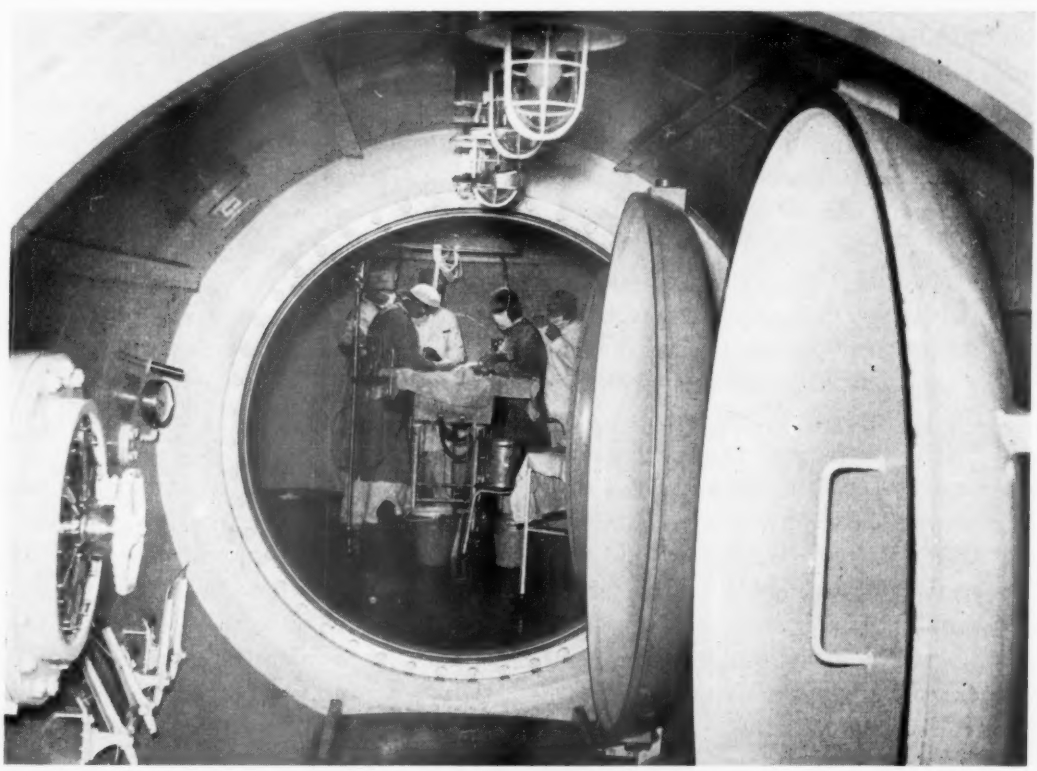

Fig. 4. Operation in the high-pressure room.

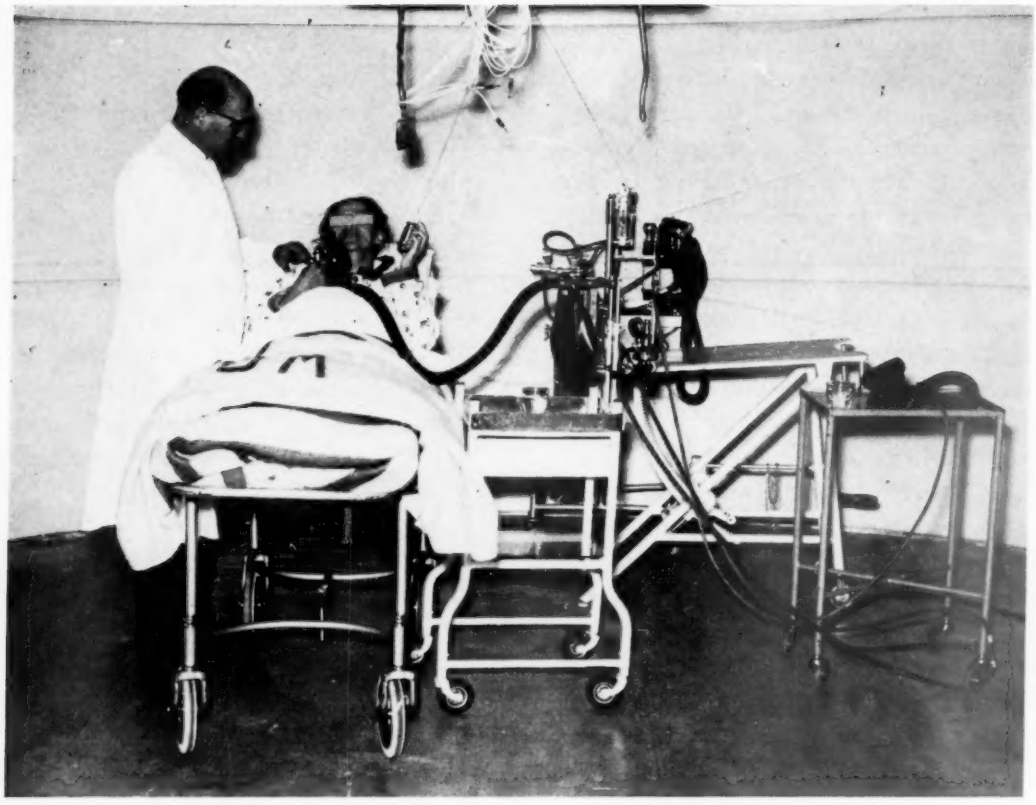

Fig. 5. Oxygen therapy in the high-pressure room.

an animal to a deep level of hypothermia without irritiating the heart muscle, and to allow an undisturbed rewarming of the body.

The latter studies have not yet been completed but we are satisfied that in the hyperpressure tank a deep hypothermia by means of surface cooling can be achieved without ventricular fibrillation. At 19 to 14.5° C. (66.2° to 58.1° F.) the dog heart was opened by atriotomy or ventriculotomy without any disturbance of the normal heartbeat, other than an occasional regular nodal rhythm. No extracorporeal circulation was required. Even clamping of the venae cavae was unnecessary. The heart could be inspected from inside for a period of half an hour or longer. It was then closed and the temperature was brought back to normal by surface warming. The animals woke up after a few hours and behaved normally the next or the second day.

Project 4. Nonoperative surgical or medical treatment has been performed in low hyperpressure tanks for over a century. The air pressure was brought up to ¼ or ⅓ of one atmosphere. It was recommended for diseases of the bronchi and lungs and for anemia, and was also thought to be of value in cases of carbon monoxide intoxication. The favorable effect of the low-grade hyperpressure on "inflammation" has been mentioned. On the other hand, however, Bert[3] considered "vibriones" very able to adjust to different concentrations of oxygen. He believed that bacteria were the first living cells on our planet and that they would be the last survivors in the distant future for that very reason.

Since several of these indications might be still of value, particularly if the pressure is increased to 3 atmospheres (absolute), we applied the method in patients with these diseases. Furthermore, drenching the tissues with oxygen might be of value in diseases in which certain parts of the body suffer from a lack of oxygen. In such cases the quantity of oxygen carried by the oxyhemoglobin is inadequate for the hypoxic tissues, but the

amount of oxygen in physical solution brought to them by means of the intercellular fluid could be of critical therapeutic significance. This is as true in patients under normal physiologic atmospheric conditions as in those breathing oxygen under high pressure in a caisson. Under the latter circumstances, however, the available quantity of oxygen carried by the intercellular fluid and offered directly to the cells is greatly increased.

We therefore treated patients who had badly impaired circulation in the limbs due to vascular diseases by allowing them to breathe oxygen for 2 hours a day, several times a week, in the hyperpressure tank. The preliminary results are promising; the pain decreased considerably. In patients with severe bedsores, the granulation of the defects could be stimulated to rapid healing by treatment several times in the caisson with oxygen inhalation. As we had anticipated, drenching the body with oxygen in the tank proved to be of great value in patients with infections which were resistant to antibiotics, particularly anaerobic infections.

Such treatment in the high-pressure tank points to an extension of oxygen therapy of a much higher intensity than is possible with oxygen breathed at normal pressures, as Binet[4] advised for various diseases.

All the studies prosecuted in the hyperpressure room are concerned with the problem of oxygen diffusion through the alveolar vascular membrane in the lungs, or with oxygen diffusion through the vascular epithelium in the tissues, or with the influence of a high concentration of oxygen on the various enzymatic processes in the cells themselves. Research has already been started on several aspects of this field.

We consider that the method of administering oxygen to patients in a hyperpressure tank, with the intention of saturating the whole body, the blood plasma, the intercellular fluid, and the cells themselves with a very high level of physically dissolved oxygen, has already proved to be of great value in experimental and clinical surgery, both operative and nonoperative. It is possible that a new field of research may be opened by this method.

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Treatment of anaerobic infections (clostridial myositis) by drenching the tissues with oxygen under high atmospheric pressure

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Oxygen administration is a well-known concept in the treatment of clostridial myositis. In the case of local application, this treatment is obviously based on the anaerobic character of the causative microorganism. Clostridia require an environment with little or no oxygen to thrive. In a high-oxygen environment they can live only with great difficulty. In the case of a clostridial infection, therefore, as much oxygen as possible is applied to the site of the inflammation in order to destroy the causative agent—a simple principle, indeed.

Oxygen can be applied locally by inflation of the diseased tissue and the adjacent tissues. This has the disadvantage, however, of giving rise to air embolism. If the inflammation affects a limb, the extremity can be enveloped in an airtight plastic sack which is then inflated with oxygen. Other methods are the application of hydrogen peroxide or activated zinc oxide to the wound.

Besides local application, general oxygenation is used, at least the literature makes repeated mention of intranasal oxygen administration, in addition to surgical and antibiotic measures, to patients with clostridial myositis. It is not stated whether the oxygen is given as a relatively normal supporting measure in the treatment of a severely ill patient, or whether it is an aimed therapeutic aid in the control of the infection.

Confining our discussion to patients with extensive clostridial myositis, that is, those showing spread on the trunk, we are inclined to think that little can be expected of local application of oxygen. What would be the use of hydrogen peroxide packs placed on the wound surface of an amputation at the hip joint if the clostridial infection had already made considerable progress over the abdominal wall? Expectations must not be high because oxygenation follows behind the advancing phlegmon. We believed that it would be more effective to enclose the advancing phlegmon, to lock it in by hyperoxygenation of the surrounding, still-unaffected tissues. We supposed that it would be possible in this way to attain, both in the phlegmon and around it, a degree of oxygenation which is incompatible with the obligatorily anaerobic character of the clostridia.

How should this total-body hyperoxygenation be effected?

At the Amsterdam Surgical Clinic, the problem of drenching the tissues with oxygen has for 4 years been a subject of investigation, particularly in connection with cardiac surgery, and some of the relevant considerations may be repeated here.[5]

Erythrocytes are of no value for total-body hyperoxygenation. Under normal conditions, even in patients with clostridial myositis, the hemoglobin already has 99 per cent oxygen saturation. Hyperoxygenation has to be effected by enlarging the quantity of oxygen physically dissolved in the plasma

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and, therefore, in all body fluids. The quantity of oxygen dissolved is exclusively dependent on, and directly proportional to, the partial gas pressure of the oxygen with which the fluid enters into contact. Under normal conditions this oxygen pressure amounts to only one-fifth of the atmospheric pressure. When 100 per cent pure oxygen is inhaled, this pressure is increased 5 times and, consequently, the quantity of oxygen physically dissolved in the plasma is increased 5 times. Should a person inhale pure oxygen while being subject to a pressure of 3 atmospheres (absolute), the quantity of oxygen physically dissolved in the plasma and the tissue fluids would be 15 times the normal value. It is on this principle that the work with the hyperpressure tank used at our clinic is based.

Working in this manner, we were able to approach the advancing infection in a patient with clostridial myositis from all sides, and to lock it in with the aid of a fifteenfold quantity of physically dissolved oxygen. We investigated this principle in guinea pigs infected with *Clostridium perfringens.*

MATERIAL AND METHOD

Group A consisted of 8 guinea pigs which were injected subcutaneously with 0.25 ml. Brewer culture of *Clostridium perfringens.* Group B was composed of 8 guinea pigs which were injected subcutaneously with 0.5 ml. Brewer culture of *Clostridium perfringens.* Group C was made up of 8 guinea pigs injected intramuscularly with 0.5 ml. Brewer culture of *Clostridium perfringens.*

Of each group of animals, 4 were submitted for 2 hours to hyperpressure in a special small tank in which the pressure was brought up to 3 atmospheres (absolute) with oxygen. The animals injected subcutaneously were submitted once to this procedure and the animals injected intramuscularly were submitted to it twice, on consecutive days.

RESULTS

The control animals of Group A were ill, and all had an ulcer. The animals treated by oxygen inhalation under hyperpressure were not ill and showed no ulcer. In Group B, the control animals were very ill, and all showed an ulcer. The animals treated with oxygen under hyperpressure were not ill, and only 1 showed an ulcer. The control animals of Group C were very ill, all had a large ulcer, and 2 animals died. The animals treated with oxygen under hyperpressure were not ill, all survived, and 2 showed an ulcer.

It was concluded from these preliminary experiments that oxygen under atmospheric hyperpressure exerts a favorable influence on clostridial infections, and that this principle can be employed in the treatment of patients with this severe disease or some other anaerobic infection.

We had occasion to treat 4 patients in this manner. Two of them were suffering from advanced clostridial myositis caused by *Clostridium perfringens (welchii).*

CASE REPORTS

Case 1. The first patient was not suffering from clostridial myositis. She was a 26-year-old woman whose case was well known to us as one of progressive gangrene of the skin which had originated from an infected surgical wound after an appendectomy performed in 1956. The condition was diagnosed as Cullen ulcer. At the time, the patient was cured after very wide excision of the diseased region, well into the unaffected tissue. In August, 1960, the left ovary and Fallopian tube were excised in the gynecological department for torsion of an ovarian cyst. After this operation, progressive gangrene of the skin again arose from the wound, showing the same features as the gangrene seen in 1956. Although the condition was more rapidly recognized this time, and aimed therapy instituted earlier, several excisions and application of antibiotics failed to arrest the process. The patient's condition was exceedingly toxic, she had a temperature of 40° C. (104° F.), and showed an ulcerating wound surface covering the entire lower abdominal region surrounded by a phlegmon which, on the left, extended as far as the axillary region. It was believed that this disease would be fatal. Results of bacteriologic examination of culture material, including anaerobic material, were negative. Nevertheless, as with the Meleney ulcer, an anaerobic infection was considered probable. As a last resort, therefore, the patient was placed in our hyperpressure tank for 2 hours daily, and submitted

to a pressure of 3 atmospheres (absolute) while inhaling pure oxygen. Within 24 hours, the phlegmon showed a less fiery red color and assumed a more macular aspect, that is, the skin areas became less markedly discolored. Besides manifesting these favorable symptoms, the patient indicated a remarkable subjective improvement. On the third day, after 4 treatments in the hyperpressure tank, the skin adjacent to the ulcer was free of discoloration. The patient was in the hyperpressure tank 5 times. After 6 days the ulcer had become a clean granulating wound surface and the temperature was 37° C. (98.6° F.). The patient made an uneventful recovery.

Case 2. A 67-year-old man was referred to our clinic with clostridial myositis which had occurred after femoral amputation for arteriosclerotic gangrene of the foot. The patient was admitted on the day after amputation at the hip joint and after antibiotics had been administered. At the time it was noticed that the gangrene had advanced to well within the psoas muscle. *Clostridium perfringens* was bacteriologically demonstrated. The process remained progressive and, at admission, the patient was stuporous and jaundiced. The wound was necrotic with bluish-black edges. Crepitation of gas was palpable throughout the lower abdomen and, on the homolateral side, it extended as far as the axilla, in which region subcutaneous fluid deposits could be made to produce lapping sounds. Within 24 hours the patient was submitted 3 times to hyperpressure of 3 atmospheres (absolute) while inhaling pure oxygen. After 2 treatments the gas had withdrawn over a handwidth, and the patient was able to articulate. On the following day he started to eat. The general condition progressively improved. Within a period of 3 days, the patient underwent 7 hyperpressure treatments, after which the clostridial myositis could be regarded as cured. Fresh granulations occurred in the wounds.

Case 3. A 13-year-old boy developed clostridial myositis 3 days after he had sustained a complicated fracture of the forearm. Broad spectrum antibiotics had been administered. The diagnosis was verified by bacteriologic examination *(Clostridium perfringens)*. Upper-arm amputation was performed elsewhere. A roentgenogram of the amputation specimen showed that gas was visible as far as the cut surface. The process remained progressive. At admission to our clinic there was crepitation of gas on the medial side of the stump. The stump was of course painful, but in addition the patient complained of violent pain in the homolateral pectoral musculature. The patient initially seemed in reasonably satisfactory condition, but 1 hour after admission he became more soporose. Once inside the hyperpressure tank he became comatose and showed transient convulsions. Despite this, a 2-hour treatment under a pressure of 3 atmospheres (absolute) with inhalation of pure oxygen was completed. On the next morning, 6 hours after institution of treatment, the patient was in good condition. Crepitation was no longer palpable in the stump, and the pain in the pectoral musculature had largely disappeared. During the first 24 hours, the patient was treated 3 times in the hyperpressure tank. He began to eat and showed progressive improvement in his general condition. In the course of 4 days, the patient was submitted to 7 treatments in the tank. He was ambulated on the third day, and was discharged in excellent condition 3 weeks after the onset of symptoms of clostridial myositis.

Case 4. A 68-year-old man was admitted with gas gangrene in the left scrotal inguinal and lumbar regions. The affected area had a width of 25 cm. and had only been incised in another hospital 3 hours before admission. There had been no débridement. The musculature of the abdominal wall did not react to mechanical stimulus. The diagnosis was verified by bacteriologic examination *(Clostridium perfringens)*. The patient was delirious; the temperature was 38.6° C. He was given penicillin treatment by us, 4 million units a day. During the first 24 hours the patient was treated 3 times in the hyperpressure tank with inhalation of pure oxygen under a pressure of 3 atmospheres (absolute). He started to eat the next day and showed progressive improvement. In the course of 5 days the patient was submitted to 8 treatments in the tank. The wound developed good granulation and the patient was discharged on the ninth day in good condition.

On the basis of our clinical observations, which are supported by experimental findings, we believe that drenching of the tissues with oxygen with the aid of the hyperpressure tank is an important innovation in the treatment of anaerobic infections.

SUMMARY

Drenching the tissues with oxygen by means of inhalation of pure oxygen in a hyperpressure tank under a pressure of 3 atmospheres (absolute) was introduced as an aid in the treatment of anaerobic infections. Four patients (Cullen ulcer and clostridial myositis) were treated successfully in this manner.

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Snake bite: treatment by isolation perfusion technique

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More people die of snake bite than die from encounters with all other wild animals combined. The most complete study of the world-wide mortality rate from snake bite indicates that more than 30,000 people die annually from envenomation.[6]

Of the existing methods of treatment for snake bite (tourniquet, incision and suction, antivenin, cryotherapy, and cortisone and ACTH), some are controversial and improvements in treatment still appear to be indicated. A major drawback to the use of antivenin in effective amounts is the subsequent occurrence of horse-serum sensitization and "serum sickness." Von Pirquet and Schick[7] demonstrated that the incidence and severity of serum sickness are directly proportional to the amount of serum injected. In their study, the injection of 100 to 200 ml. of serum resulted in an incidence of serum sickness of 85 per cent (Fig. 1).

Since 98 per cent of snake bites are on the extremities,[4] an evaluation of isolation perfusion techniques was carried out with antivenin as the perfusate. This provided a method of delivering a large quantity of antivenin to the bitten extremity while minimizing systemic toxic effects.

The venom used in the experiments was obtained by "milking" a collection of red rattlesnakes *(Crotalus ruber ruber)* at 3-week intervals. "Milking" was effected by having the snakes bite a latex rubber hose. The discharged venom was then collected in an attached test tube. The venom was centrifuged at 2,500 r.p.m. at 2° C. for 2 hours, and the supernatant was vacuum-dried and kept refrigerated at 4° C. in a desiccator. Pooled snake venom was used in order to maintain a constant toxicity level. The venom was reconstituted by dissolving approximately 75 mg. of venom in 1 ml. of normal saline solution at the time of each experiment.

Toxicity studies were carried out on 13 adult mongrel dogs which weighed between 12 and 20 kilograms. The animals were anesthetized with 20 mg. per kilogram of pentobarbital sodium and injected subcutaneously in the hind leg with various amounts of venom. The minimum lethal dose was determined to be 3.5 mg. per kilogram of body weight. Death had to occur within 3 days of injection to be considered due to envenomation.

The perfusate incorporated Wyeth antivenin.* This is prepared by the immunization of horses with a mixture of venoms obtained from a variety of snakes in the following percentages:[1] tropical rattlesnake

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*Antivenin (Crotalidae) Polyvalent (North and South American antisnakebite serum) was donated by Wyeth Laboratories, Philadelphia 1, Pa.

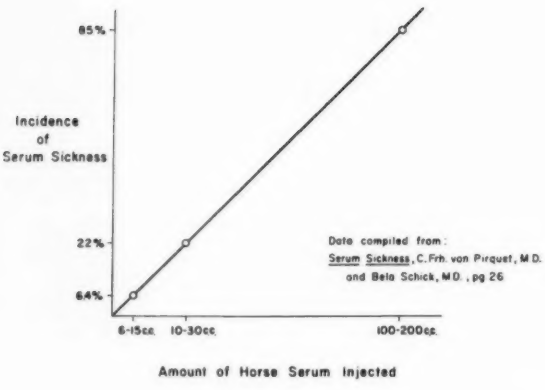

Fig. 1

(Crotalus terrificus), 33.33 per cent; Maximillian's pit viper *(Bothrops neuweidii),* 16.67 per cent; fer-de-lance *(Bothrops atrox),* 16.67 per cent; Western diamondback rattlesnake *(Crotalus atrox),* 16.67 per cent; and Eastern diamondback rattlesnake *(Crotalus adamenteus),* 16.67 per cent. Each milliliter of the Wyeth antivenin now produced is capable of neutralizing 3 mg. of rattlesnake venom.[3]

Two dogs were anesthetized with 20 mg. per kilogram of pentobarbital sodium. A hind leg of each was injected with 3 M.L.D. of pooled venom and a tourniquet was loosely applied to the leg. Thirty minutes after the venom had been injected, femoral vessels were exposed and 2 mg. per kilogram of heparin was given intravenously. The vessels were then cannulated and the previously placed proximal tourniquet was tightened. Isolated limb perfusion was carried out by means of the Sigmamotor pump and Abbott* bubble bag oxygenator by a technique similar to that employed by Creech[2] for the treatment of malignant tumors, with antivenin incorporated in the perfusate in place of tumoricidal drugs. The system was washed with 300 ml. of heparinized fresh blood in each instance. Each dog perfused in this manner died in shock secondary to massive hemorrhage into the perfused leg. It was postulated that the local increased capillary fragility produced by the venom made the vascular bed of the extremity more susceptible to pressure changes inherent in the pump perfusion procedures with subsequent capillary disruption and hemorrhage.

In an attempt to reduce postperfusion bleeding, decrease surgical technicalities, and establish a readily available method of perfusion which would require only a basic amount of equipment, we devised a simplified needle cannulation with syringe perfusion method. Fourteen dogs were anesthetized with 20 mg. per kilogram of pentobarbital sodium, and 3 M.L.D. was injected subcutaneously into the distal part of the hind leg. A tourniquet was loosely applied high on the leg and after a period of from 30 minutes to 1½ hours, the femoral vessels were exposed and cannulated by means of a No. 20 needle in the artery and a No. 15 needle in the vein. Heparin, 2 mg. per kilogram of body weight, was given intravenously. Both vessels were clamped proximally and the tourniquet was tightened. One hundred twenty milliliters of antivenin was mixed with 250 ml. of sterile saline solution and injected distally into the arterial cannula by means of a syringe. Equal aliquots of blood were concomitantly removed through the venous cannula. After perfusion, the system was washed with 250 ml. of heparinized blood. The dogs were then transfused with another 250 ml. of blood upon release of the tourniquet. The total operating time was less than 1 hour.

After perfusion, no further extension of edema or local hemorrhage occurred in 12 of the 14 dogs treated (Table I). During the early postoperative period, the dogs were alert and progression of the local proteolytic reactions was halted. In no case did the hemorrhagic edema extend proximal to the tourniquet. The thirteenth dog developed a femoral arteriovenous fistula and died in 12 hours. The other dog was given hydrocortisone locally with subsequent marked local tissue necrosis and infection of the leg, and death. The addition of local incision with suction and local injection of 10 ml. of antivenin to the regimen questionably reduced local tissue necrosis.

*Pulmo-pak, Abbott Laboratories, North Chicago, Ill.

To determine the amount of spillover into the systemic circulation, Cr^{51}-tagged red cells were added to the perfusate in 2 dogs. After 30 minutes of perfusion, the amount of spillover was found to be 21 per cent. The amount of time spent in actual antivenin perfusion was less than 15 minutes.

Nine control dogs (Table II) were envenomed in the same manner and treated by means of the current clinical methods of therapy, including tourniquet isolation, incision with suction, local injection of antivenin, intravenous administration of antivenin, and cryotherapy. Tissue necrosis and limb swelling were much more marked and mortality rate higher in the animals treated by combinations of the current clinical methods of therapy than in those which underwent perfusion.

The isolation perfusion technique with

Table I

Dog No.	*Weight (Kg.)*	*Amount of venom injected (mg.)*	*Interval between injection and perfusion (min.)*	*Amount* of antivenin perfused (ml.)*	*Adjuncts to isolation perfusion*	*Results*
1	14.7	155	45	120		Ulceration at injection site after 2 days
2	15.0	158	40	120		Tissue destruction and bleeding at injection site
3	12.5	133	30	120	Local antivenin, 10 ml.	No bleeding from injection site until 48 hours later
4	11.5	121	30	120	Incision and suction	Developed A-V shunt at time of perfusion and died 13 hours later
5	13.5	142	30	150	Incision and suction, 20 ml. antivenin I-V, local antivenin, 10 ml.	Leg swollen twice normal size, small area of ulceration
6	13.5	142	40	120	Local hydrocortisone	Died 37 hours later, marked infection and slough of leg
7	18.5	194	35	150	Local hydrocortisone	Marked slough and infection
8	22	231	30	100	Incision and suction; local antivenin, 10 ml.	Slough size of dollar at site of injection after 6 days
9	13.5	142	45	100	Local antivenin, 10 ml.	Minimal bleeding at site of injection
10	17.0	179	45	120		Minimal ulceration at injection site
11	14.7	154	45	120		Leg swollen but no apparent destruction of tissue until 24 hours later
12	16.2	170	45	120		Moderate tissue destruction size of half dollar
13	13.3	140	90	120		Tissue destruction not apparent until 1 day later, then moderate
14	17.8	187	90	120		Leg swollen 1½ times normal size, minimal ulceration

*Total perfusate = 3 times volume of antivenin (the remainder was sterile saline).

Table II

Dog No.	*Weight (Kg.)*	*Amount of venom injected (mg.)*	*Tourniquet**	*Incision and suction**	*Cryotherapy*	*Local antivenin† (10 ml.)*	*Intravenous† antivenin (ml.)*	*Results*
1	18.2	191	x	x			20	Died, 36 hr., hemorrhagic edema progressed to midabdomen, leg 3 times normal size
2	17.3	182					20	Died, 23 hr., much oozing of blood from injection area
3	17.0	179	x	x		x	210	Survived, swelling progressed proximal to leg
4	17.1	180			x			Died, 8 hr., swelling not markedly decreased from nontreated dogs
5	16.0	168			x			Died, 10 hr., swelling not markedly decreased from nontreated dogs
6	13.5	142	x	x		x	25	Survived, very toxic, leg 3 times normal size
7	14.2	149	x	x				Died, 38 hr., much slough including muscles of leg
8	12.5	131		x		x		Died, 27 hr., leg 3 to 4 times its normal size
9	18.9	199				x	20	Died, 31 hr., much local slough, leg 3 times normal size

*Utilized 5 minutes after envenomation.
†Utilized 30 minutes after envenomation.

antivenin as the perfusate markedly improved the mortality and morbidity statistics in the experimental groups as compared to the control animals, and utilization of this technique in clinical trials seems to be indicated.

DISCUSSION

If this technique were adapted to human subjects, the amount of spillover should be much less than that determined in dogs, since better tourniquet methods are available for human extremities. It should be less than the 10 per cent determined by Monaco and Austen[5] due to decreased pressure and time of actual perfusion.

This technique is so simple that someone with minimal surgical training and equipment should be capable of performing it.

The time which elapses between snake bite and the start of the isolation perfusion with antivenin in human beings can probably be at least 5 times that of dogs because of the proportionate difference in limb length.

A tourniquet which is tight enough to stop lymphatic and venous, but not arterial, flow should be kept 1 inch proximal to the advancing margin of discoloration and edema until isolation perfusion is performed.

The patient should be kept as calm as possible and the bitten extremity should be kept dependent.

Antibiotics and tetanus therapy should also be used in the treatment of snake bite in human patients because of the virulent flora found in the snake's mouth.

SUMMARY

1. In certain instances current methods of snake bite therapy are inadequate.

2. Toxicity studies have been carried out in dogs by means of pooled rattlesnake venom. The minimum lethal dose was determined to be 3.5 mg. per kilogram.

3. Nine dogs injected with 3 M.L.D. of rattlesnake venom into the hind leg were treated by conventional methods of therapy. Death ensued in 7 dogs.

4. By means of isolation and simple needle perfusion with a solution of antivenin, 12 of 14 envenomed dogs were successfully treated.

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Tolerance to intravenously administered fat emulsions

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Patients who are temporarily unable to eat for any reason often need more calories than can be furnished intravenously by any of the currently available solutions. The high caloric content of fats makes intravenously administered fat emulsions an excellent source of energy for such patients, provided that a satisfactory nontoxic fat emulsion is available. Work in this laboratory has been directed toward the development of an emulsion which can be given safely in larger quantities than those currently used. The emulsions now available are recommended for limited intravenous administration amounting to approximately 10 ml. per kilogram of body weight per day, or approximately 1,100 calories per day to a 70-kilogram patient. This limitation is due to the toxicity associated with the use of larger quantities or longer administration of these emulsions. Preliminary results with the emulsion developed in this area, the SR emulsion, have shown that it is tolerated by dogs in the massive dosage of 50 ml. per kilogram per day. This report presents the comparative findings concerning the administration of SR and Lipomul I.V.

MATERIALS AND METHODS

This is a study of the changes observed in dogs infused with massive intravenous doses of two fat emulsions, SR emulsion* and Lipomul I.V.† The constituents of the two emulsions are shown in Table I. The dogs were given Purina Dog Chow and water throughout the period of study.

Some modifications were made in the SR emulsion as the study progressed and most of the results presented here were obtained with the more purified form of the emulsion.

A No. 8 Fr. polyvinyl Pharmaseal tube was inserted into the external jugular vein and exteriorized on the dorsum of the neck. Infusions were conducted 5 days a week at 40 drops per minute. The standard infusion program was to administer 30 infusions to each animal regardless of the condition of the dog prior to any infusion. One day after the thirtieth infusion, the dog was either sacrificed and autopsied or returned to the animal colony for long-term observation. Any animals that died during the infusion program were autopsied.

Blood samples and whole body weights were taken every Monday and Friday prior to infusion. Sufficient blood was drawn to

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†Lipomul I.V. was supplied by The Upjohn Company, Kalamazoo, Mich.

Table I. *Composition of the fat emulsions*

	SR (%)	*Lipomul I.V. (%)*
Lecithin	—	1.2
Pluronic F68	0.3	0.3
Dextrose	5.0	4.0
Polyethylene glycol stearate	1.2	—
TEM 4 T	0.3	—
Cottonseed oil	15.0	15.0
Water	78.2	79.5

provide serum for electrophoretic studies, hemograms, and Bromsulphalein, blood urea nitrogen, and direct and indirect bilirubin determinations which were conducted with standard laboratory procedures.

Autopsy specimens were preserved in alcohol and formalin. Tissues from each animal were sent to the United States Army Medical Nutrition Laboratory for an analysis of the intravenous fat pigment.

RESULTS

The mortality rates and the number of infusions tolerated (Table II) show a superiority for the SR emulsion at the higher dosage rates. Nine of 15 animals survived long-term infusions with SR at doses of 40 or 50 ml. per kilogram of body weight, whereas no animal survived Lipomul I.V. infusions at a rate higher than 30 ml. per kilogram.

When the emulsion was administered at the higher dosage levels, dogs on SR maintained their weight, while the dogs on Lipomul I.V. lost weight. There was a noticeable decrease in food intake with either emulsion.[2]

Vomiting was a prominent feature in all animals which received fat intravenously. It usually occurred during the infusion period, but was never of sufficient magnitude to cause death by either fluid or electrolyte imbalance.

Four dogs that received Lipomul I.V. and 1 that received SR had gross blood in the stool. In all 5, an upper gastrointestinal source of bleeding was found at autopsy. Duodenal ulcers were present in 3 and in 2 there were petechial hemorrhages in the duodenum or prepyloric area. None of the animals that received the improved SR at 50 ml. per kilogram had gross blood in the stool during the experiment or evidence of gastrointestinal ulceration at autopsy.

Three animals that received Lipomul I.V. had a cough and dyspnea during the last few days of fat administration. All three had great pleural effusions.

The most significant blood abnormality of the dogs given fat intravenously was a drop in hematocrit and hemoglobin. This occurred in all animals, but particularly those that received fat at dose rates of 40 and 50 ml. per kilogram. The anemia was normocytic and normochromic and was more severe in dogs given Lipomul I.V. than those given SR (Fig. 1). The reticulocyte response averaged 3.0 per cent from a control value of 0.8 per cent. White blood cell counts generally rose 3 to 4 times the preinfusion levels during the first half of the infusion period. There was a gradual return to normal in dogs that survived, whereas death during the infusion period was often assoicated with a leukocytosis.

Lipemia was noted in 3 of the 5 dogs that died during the infusions of 50 ml. per kilogram of SR.

Table II. *Comparison of survival rate and weight changes of dogs given SR fat emulsion and Lipomul I.V.*

No. of dogs	*Dose rate (ml./Kg.)*	*Avg. No. of infusions*	*Range of weight changes (%)*	*Mortality rate (%)*
Series A (Lipomul I.V.)				
2	30	30	+12	0
6	35-40	16	−25 to −6	100
3	50	12	−25 to −6	100
11				82
Series B (SR)				
2	30	30	+12	0
6	40	28	− 9 to +36	16
9	50	22	−15 to +15	55.5
17				35

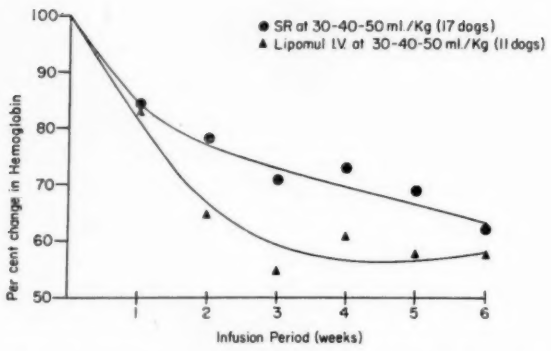

Fig. 1. The anemia and its rate of development associated with daily intravenous infusion of fat emulsions into dogs.

Results of direct and total bilirubin determinations remained within normal limits in dogs that survived administration of SR at 50 ml. per kilogram per day, and in dogs receiving smaller doses of either emulsion. Two of the 5 dogs that died at 50 ml. per kilogram had an elevated bilirubin level. Bromsulphalein retention was likewise within normal limits except in 1 dog with an elevated bilirubin level.

Results of serial determinations of serum amylase, blood sugar, blood urea nitrogen, prothrombin time, and Lee-White clotting time remained within normal limits.

Autopsy. One dog that survived 30 infusions with Lipomul I.V. and another with the SR emulsion at 30 ml. per kilogram were sacrificed after the last infusion. In each case, all organs were grossly normal. The presence of the intravenous fat pigment in the liver, spleen, lymph nodes, and bone marrow was the only abnormal microscopic finding.

The 9 dogs that received Lipomul I.V. at dose rates over 30 ml. per kilogram died prior to completion of the 30 infusions. The liver was enlarged and greasy in each. There was microscopic evidence of severe fatty degeneration. Eight dogs had pneumonitis and 6 had pleural effusions. Three dogs had duodenal ulcers, 1 had a gastric ulcer, and 1 a hemorrhagic gastritis. Two dogs that received the old form of SR emulsion had autopsy findings similar to those of dogs which received Lipomul I.V.

Nine animals received 50 ml. per kilogram of the purified SR. One of the 4 survivors was sacrificed after completion of the thirtieth infusion and no abnormalities were noted grossly or microscopically. The animals that did not survive had fatty changes in the liver microscopically, but not grossly. The intravenous fat pigment was found in the reticuloendothelial tissues. In no case was the fat overloading syndrome seen, nor were any peptic ulcers found.

DISCUSSION

There is a need for a safe fat emulsion that can be given intravenously in sufficient quantity to provide 30 to 40 calories per kilogram per day to patients over a prolonged period of time. Such an emulsion would be an invaluable aid in the care of patients who are unable for any reason to take sufficient nutrition by the oral route. But such an emulsion would be helpful only if it could be given in large quantities over a long enough period of time to allow correction of the particular cause of impairment of oral intake, and provided the emulsion could be given without producing any toxic effects of its own. In our experience the emulsion currently available has not been able to meet these requirements and therefore we have attempted to develop a new and different emulsion which would fulfill the requirements we have set.

The maximum volume recommended for infusion of the currently available fat emulsion, Lipomul I.V., is approximately 15 ml. per kilogram per day with a maximum of 14 infusions in any one patient. This provides only about 25 calories per kilogram per day, and cannot be continued beyond 14 days without some risk. In the laboratory it has been possible to increase the infusion dose to 30 ml. per kilogram per day with Lipomul I.V. (48 calories per kilogram per day), but any further increase has been associated with lethal results.

In an attempt to test the safety of various emulsions, we adopted the plan of infusing the fat emulsions at dosages higher than those which would be recommended clinically in order to bring out any latent

toxicity and thus more clearly define the safe limits of infusion as well as determine whether or not such an emulsion would be of value in providing all the calories that would be required by a patient unable to tolerate any oral intake. Without suggesting that such massive dosages would be indicated clinically, it has been possible to infuse dogs with fat emulsions at rates which provide up to 80 calories per kilogram for 30 days, without evidences of toxicity that would necessitate cessation of infusion.

The experience reported by various authors with long-term intravenous infusion of fat emulsions to patients shows a striking similarity in toxic manifestations in human beings and dogs. This justifies the use of the dog as an experimental animal for the study of fat overloading syndrome. Our results and those of Zilversmit[5] and Meng[3] show that dogs can develop evidences of the fat overloading syndrome—vomiting, anemia, fatty infiltration of liver and spleen, abnormal liver function, gastrointestinal bleeding, intravenous fat pigment deposition, and death. Variation in the emulsifier-stabilizer system has been shown to markedly improve the tolerance to the amount of fat infused. Dogs have been shown to metabolize as much as 7.5 Gm. of fat per kilogram of body weight per day, which is equivalent to the maximum tolerance thus far reported.[5]

The development of anemia during the administration of fat is an undesirable side effect that would be badly tolerated by a patient who is already in need of some nutritional supplementation. Since this has been observed in both human beings and experimental animals, it is a problem that cannot be ignored. It was previously thought that gastrointestinal bleeding could explain the anemia, but although ulceration and gastrointestinal bleeding have not been observed with the more purified SR emulsion, anemia has continued to appear. Hemolysis has been strongly suspected but as yet has not been definitely implicated as the cause of the anemia. Both Artz[1] and Watkins[4] have noted decreases in hemoglobin in most of the patients on prolonged intravenous fat therapy. The anemia does not persist in the experimental animal once the infusions are terminated, which would suggest that the anemia is not due to some permanent depression of the bone marrow, but is more likely the result of some temporary toxic or hemolytic effect of the fat or one of its components. Dogs have been followed for up to 19 months after the last infusion, and generally have shown a recovery from the anemia. During this period of observation there have been no deviations from the normal in Bromsulphalein, blood urea nitrogen, or serum bilirubin values.

The intravenous fat pigment has been found in the reticuloendothelial system of human beings and dogs, but the significance of this pigment has not been determined. Serial liver biopsies taken from the dogs up to 19 months after their last infusion suggest that the intravenous fat pigment is being eliminated slowly from the tissues, and that there is no evidence of any chronic reaction to the pigment deposition, regardless of what the pigment is.*

A fat emulsion for intravenous administration would be a valuable addition to the therapy of patients in need of additional nutritional supplementation, provided the fat did not introduce new dangers of its own, and provided there was a relatively simple means of detecting when the danger zone of administration was approaching. The best sign yet observed as evidence of approaching toxicity remains the presence of persistent lipemia. Lipemia has been noted in most of the dogs that have died from the overloading syndrome after the intravenous infusion of either of the fat emulsions studied in this project. No other clinical or laboratory finding has been as consistently associated with impending death as this one.

*Since the preparation of this manuscript, additional liver biopsies have been taken. Tissues from dogs that had received their last infusion of fat emulsion 2.5 years previously showed the presence of scar tissue, apparently a consequence of intravenous fat pigment deposition. This significant change will be discussed in a later publication.

These studies have demonstrated that tolerance to intravenous fat emulsions can be increased by employing a proper emulsifier-stabilizer system. If clinical trial of the new emulsion (SR) confirms the laboratory findings, a new, safer, and better-tolerated fat emulsion for intravenous administration should be available for clinical use in cases in which a high parenteral caloric intake is needed.

SUMMARY

1. Two fat emulsions were infused intravenously into dogs to study their tolerance to massive infusions of fat emulsions.

2. Fifteen dogs were infused with the SR emulsion at dose rates of 40 and 50 ml. per kilogram per day. Five of 6 dogs survived a 30-infusion period at 40 ml. per kilogram, 3 of 9 survived 30 infusions at 50 ml. per kilogram, and 1 survived 25 infusions at 50 ml. per kilogram. Eight dogs infused with Lipomul I.V. at similar dose rates all died during the infusion period.

3. One of the 3 dogs which survived 30 infusions of SR at 50 ml. per kilogram was sacrificed 1 day after the last infusion. There were no gross or microscopic abnormalities. In contrast, dogs that died during the infusion period with either emulsion exhibited marked changes in the liver and lungs and had changes less frequently observed in the spleen, pancreas, and kidneys.

4. Dogs which survived the infusion program have been observed for up to 2 years. Hemoglobin has returned to normal and the results of Bromsulphalein and blood urea nitrogen determinations have remained within normal limits.

5. A fat emulsion, the SR emulsion, has been developed which can be infused into dogs over extended periods at a rate of 50 ml. per kilogram per day, an amount 7 times that recommended clinically.

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Mammary infarcts associated with pregnancy presenting as breast tumors

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Unnecessary radical mastectomies have been performed in the past for benign tumors which have become infarcted with consequent clinical simulation of carcinoma of the breast.[4] We have encountered 3 instances of infarction of physiologically hyperplastic mammary tissue associated with pregnancy which presented clinically as breast neoplasms. Such cases have not been previously reported. The tumors appeared in the last month of gestation in 2 cases. In 1 case the tumor was detected several days after delivery. The lesions were excised after delivery in all cases and were formed of physiologically hyperplastic mammary tissue with extensive coagulative necrosis. The clinically palpable masses corresponded to the tumors formed of necrotic tissue. The pregnancies in all 3 cases were uneventful.

CASE REPORTS

Case 1. A 33-year-old Negro female, gravida iii, para i, who had had one abortion, was admitted to the hospital on June 30, 1958, in labor at term. The pregnancy had been uneventful until a right breast mass was noted about 4 weeks prior to admission. The woman had gained 27 pounds.

The breast mass was located in the lower inner quadrant and was freely movable, nontender, and firm. It was 3.5 cm. in greatest dimension. The clinical diagnosis was fibroadenoma. Laboratory studies were noncontributory.

A cesarean section was performed on June 30, 1958, because of a previous section after prolonged labor. The infant was a healthy, full-term female. The postoperative course was complicated by a urinary tract infection on the twelfth postpartum day. The breast mass had decreased in size between the time of admission and the time of excision, which was 17 days later.

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On section, the specimen exhibited a discrete mass of rubbery yellow tissue. A frozen section was interpreted as a benign unclassified lesion. Microscopic sections showed diffuse coagulative necrosis of mammary lobules (Fig. 1, *A*). The necrotic tissue was rimmed by a cellular and vascular fibrous tissue containing round cells (Fig. 1, *B*). No vascular lesions were identified. The lesion was interpreted as being an infarct of physiologically hyperplastic mammary tissue. The intact portions of tissue showed regressive postpartum changes (Fig. 1, *C*).

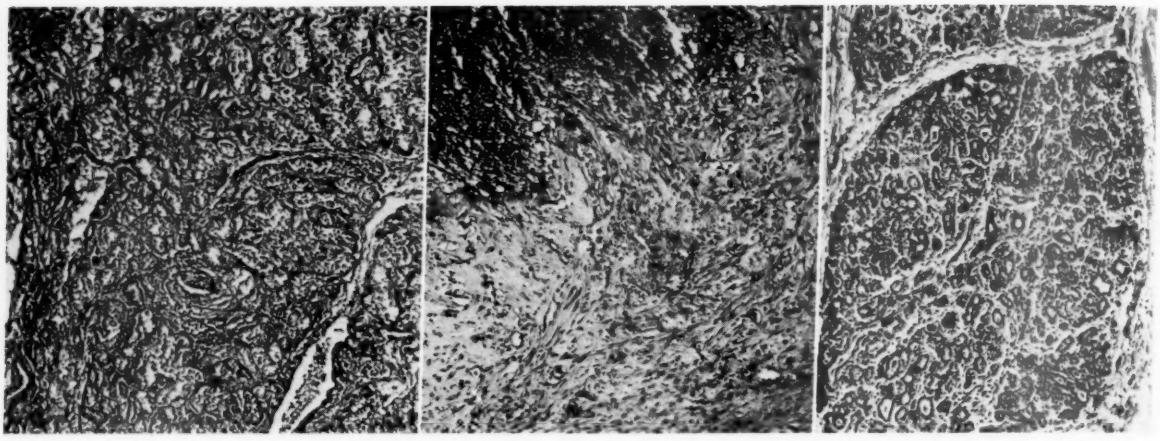
Case 2. A 23-year-old white female, gravida iii, para ii, was admitted at term on Nov. 11, 1958, and delivered of a healthy female infant. The pregnancy had been uneventful. The woman had gained 20 pounds.

Three weeks prior to delivery, a mass had been noted in the right breast. It was palpated above the nipple and was 3.0 cm. in greatest dimension. It was firm, nontender, and freely movable. There was no axillary lymphadenopathy. The preoperative diagnosis was fibroadenoma of the breast. The tumor was surgically excised on the seventh postpartum day.

On examination of the cut surface the lesion appeared as a firm rubbery discrete mass of yellow tissue with small foci of hemorrhage. Microscopic examination revealed widespread coagulative necrosis of proliferated mammary tissue with focal hemorrhages (Fig. 2, *A*). Organization of the necrotic tissue by fibrous tissue was apparent peripherally and irregularly within the necrotic zone (Fig. 2, *B*). Portions of intact breast tissue were found around the rim of the area of necrosis and as islands within it (Fig. 2, *C*). There were no vascular lesions. The pathologic process was interpreted as being an infarct of physiologically hyperplastic mammary tissue.

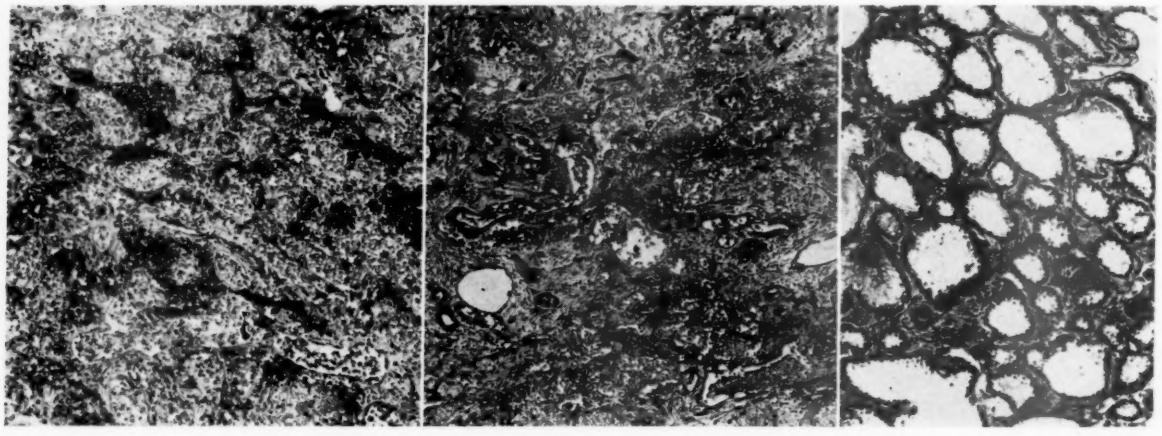
Case 3. A 26-year-old white female, gravida ii, para i, was admitted at term on Nov. 30, 1959, and delivered of a healthy female infant. The pregnancy had been uneventful. She had gained 21 pounds.

Examination on the sixth postpartum day showed a right breast mass in the lower inner



A *B* *C*

Fig. 1. Case 1. *A,* Zone of coagulative necrosis with preservation of architectural outlines of mammary alveoli. *B,* Peripheral organization of infarcted tissue in upper left area by vascular fibrous tissue. *C,* Intact mammary tissue with regressive postpartum changes. (Hematoxylin and eosin; ×65; reduced ¼.)



A *B* *C*

Fig. 2. Case 2. *A,* Zone of coagulative necrosis with foci of hemorrhage. *B,* Organization of infarcted tissue. Note persistence of altered intact mammary alveoli. *C,* Appearance of intact mammary tissue. (Hematoxylin and eosin; ×65; reduced ¼.)

quadrant. It measured approximately 1.0 cm. in greatest dimension and was firm, mobile, and nontender. The mass was surgically excised on Dec. 22, 1959.

Most of the specimen, which measured 3 cm. in greatest dimension, consisted of grossly normal mammary tissue surrounding a discrete, firm yellow area measuring 0.8 cm. in diameter. A frozen section was interpreted as a benign lesion. Microscopic study showed a discrete area of coagulative necrosis of mammary tissue (Fig. 3, *A*). Peripherally there was evidence of fibroblastic proliferation. The surrounding intact mammary tissue showed regressing postpartum mammary tissue (Fig. 3, *B*). This lesion was interpreted as being an infarct.

PATHOLOGY AND ETIOLOGY

The zones of necrosis observed in all 3 cases were typical of coagulative necrosis characterized by a loss of cellular detail with preservation of the architectural outlines of mammary alveoli. One patient (Case 2) showed foci of hemorrhage in the necrotic tissue. Coagulative necrosis is the classical change seen in infarcted tissues exclusive of

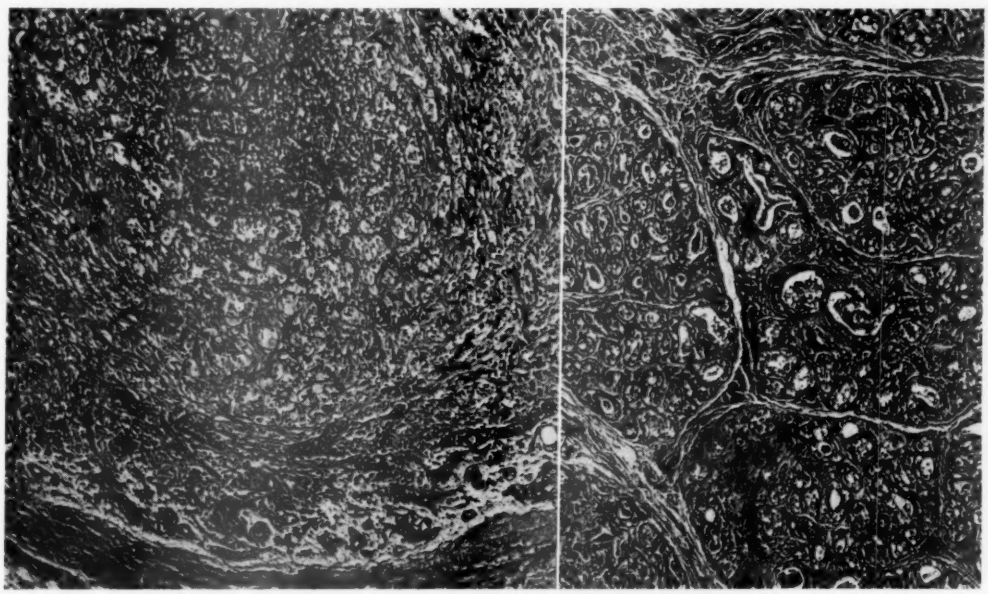
the central nervous system. There was no clinical or anatomic evidence of any form of infection that might conceivably have caused a similar type of necrosis. Cases of syphilitic gummas of the breast have been reported[7] which showed coagulative necrosis, but demonstrated the characteristic endarteritis and were not related to pregnancy. None of our patients had positive results of a serologic test for syphilis (VDRL).

The etiology of infarcts of proliferated mammary glandular tissue in late gestation observed here is not known. There was no history of trauma in any of the cases or any suggestion that poorly fitted, tight brassieres were worn. No vascular lesions were demonstrated. In the absence of any vascular lesions, we can only postulate that there was some mechanism which caused relative vascular insufficiency in an organ with heightened proliferative and metabolic activity.

DISCUSSION

A review of the literature revealed no reports of cases comparable to the three described here. Infarction of breast tumors has been recognized. Ackerman[1] has observed infarction of carcinomas of the breast and of intraductal papillomas. We have observed an example of infarction of isolated proliferated lobules in sclerosing adenosis (Fig. 4). The case illustrated is that of a 31-year-old woman with a 10-month history of a breast mass, clinically diagnosed as a fibroadenoma. Delarue and Redon[4] reported 6 cases of fibroadenoma with superimposed infarction. The tumors clinically simulated carcinoma because of hardness, fixation, evidence of inflammation, and axillary lymphadenopathy. The clinical certainty of a diagnosis of carcinoma was maximum in 4 of their patients, who were subjected to mastectomy without the benefit of a prior biopsy.

Bamberger[2] reported an instance of postpartum gangrene of the entire left breast in a 26-year-old woman as a complication of puerperal sepsis. The breast was amputated prior to death with little or no bleeding. Katz[6] described postpartum symmetrical gangrene of the nipples in a 22-year-old woman. In his case, the spontaneous delivery of a full-term infant was followed by retention of the placenta, which was manually expressed. The drugs which were administered included pituitrin, camphor, caffeine and sodium benzoate, Adrenalin, and a de-



A *B*

Fig. 3. Case 3. *A*, Infarcted mammary tissue in upper field rimmed by organizing fibrous tissue containing foamy histiocytes and scattered intact mammary alveoli peripherally. *B*, Intact mammary tissue with regressive postpartum changes. (Hematoxylin and eosin; ×65.)

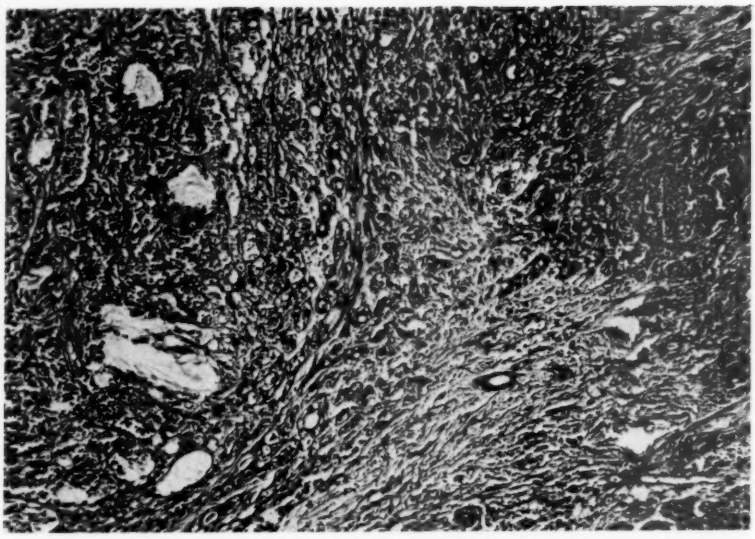


Fig. 4. Incidental finding of focal infarction of proliferated lobule in a case of sclerosing adenosis. This can be mistaken for carcinoma. (Hematoxylin and eosin; ×65.)

rivative of ergot. The patient began to nurse after 1 day. Necrosis of the nipples appeared on the third postpartum day and progressed without pain or signs of inflammation until the tenth day when one necrotic nipple detached spontaneously and the other was easily removed with forceps. This was followed by healing with epithelization of the ulcerated nipple areas. Histologic study of the tissue showed necrosis and thrombosed blood vessels. The author suggested drug-induced vasospasm or an unusual variant of Raynaud's phenomenon as possible factors in this unique process.

Examples of infarction of the breast unrelated to pregnancy have been documented in association with mitral stenosis and congestive heart failure. Gruber's[5] case was one of a 42-year-old woman with severe mitral stenosis who died in congestive heart failure with discoloration and a large mass in the right breast. Autopsy demonstrated a massive infarct of the breast due to thrombosis of the axillary vein and its tributaries draining the breast. Multiple pulmonary infarcts were also found. Caniggia[3] described an infarct which occurred in the breast of a 42-year-old woman with mitral stenosis. Its evolution into a mass took 3 weeks. Examination after 1 year showed disappearance of the mass. This lesion was not documented by histologic examination.

SUMMARY

Three cases of infarcts of physiologically hyperplastic mammary tissue appearing in association with pregnancy are presented. The lesions appeared in the last month of pregnancy in 2 cases and during the week after parturition in 1 case. The lesions presented as discrete breast tumors which were excised for diagnosis.

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Schönlein-Henoch syndrome

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Schönlein-Henoch syndrome is an uncommon disease. Nevertheless, it has received widespread notoriety as a cause of abdominal pain in children.

Historically, the two physicians after whom the disease is named described only part of the clinical features which are recognized today. Schönlein (1837) mentioned the manifestations in the joints and skin while Henoch (1874) emphasized the abdominal as well as the skin changes. Only later was it realized, mainly through the writings of Sir William Osler,[15, 16] that all three groups of symptoms could occur in the same patient and that the abdominal symptoms frequently simulated an acute abdominal condition. During the same period other authors pointed out the frequency of serious abdominal complications resulting from this disease, the most notable being small bowel intussusception.

After publication of these early reports, the term "Schönlein-Henoch syndrome" was used rather loosely in describing a wide variety of purpuric conditions irrespective of their clinical and pathogenic background. During the last 10 years, however, Schönlein-Henoch syndrome has been more clearly defined by some authors[7, 10, 14] as a nonspecific vasculitis. Such a definition suggests a systemic vascular disorder. Because Schönlein-Henoch syndrome may present surgical problems, it is the purpose of this paper to review 5 cases seen at the University Hospitals and to discuss the surgical features in the light of recent observations concerning etiology and pathogenesis.

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MATERIAL

The hospital records of 5 patients whose clinical manifestations were consistent with the diagnosis of Schönlein-Henoch syndrome have been reviewed. Briefly, each patient showed either skin, joint, and/or abdominal symptoms during the course of their illness. In addition, hematuria was noted in 2 cases. Of the 5 patients, 3 were females and 2 were males. Their ages ranged from 2 to 16 years, and 4 of the children were between 2 and 5 years of age.

Four children were primarily pediatric problems and were admitted to the University Hospitals because of recurrent attacks of Schönlein-Henoch syndrome. Each child had suffered 2 or more episodes of Schönlein-Henoch syndrome at intervals of 10 to 30 days prior to their admission. Each attack had been characterized by what the parents called a skin rash. However, in only 2 instances was a purpuric change noted. In addition, joint pain, crampy abdominal pain, diarrhea (bloody in 2 cases), nausea, vomiting, and generalized malaise were described. In each of the patients the symptoms persisted for from 48 hours in 1 child to as long as 6 days in another. According to the referring physicians the abdominal manifestations were minimal and surgical consultation was not considered necessary. In addition, each child had an upper respiratory infection that preceded the onset of the initial illness. In 2 instances beta hemolytic streptococci were cultured from the nasopharynx, but no grouping or typing of the organisms was done. As each of the children was seen for medical purposes, their hospital courses will not be discussed except that each child was extensively studied from a

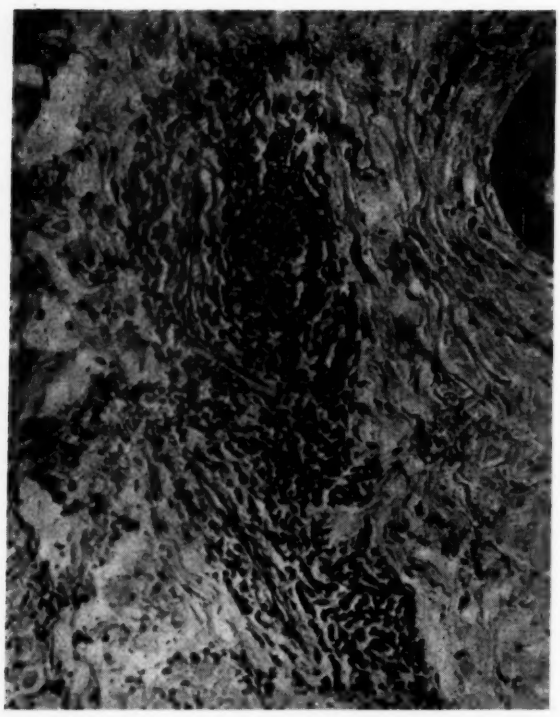

Fig. 1. Microscopic section of a skin lesion in Schönlein-Henoch syndrome. This section shows the perivascular infiltration about a small arteriole. (From Gairdner, D.: The Schönlein-Henoch Syndrome, Quart. J. Med. 17: 95-123, 1948.)

hematologic standpoint and results of all tests, particularly those pertaining to blood coagulation, were within normal limits.

The fifth case will be discussed in detail because the abdominal manifestations were of a surgical nature.

CASE REPORT

E. L., a 14-year-old girl, was known to suffer Schönlein-Henoch syndrome and had been admitted to the University Hospitals on 3 different occasions because of this condition. On one occasion elsewhere, the abdominal symptoms suggested an acute appendicitis and the patient underwent an appendectomy. Her present illness began 24 hours prior to admission and was initiated by crampy, lower abdominal pain followed by diarrhea, nausea, and vomiting. Within 36 hours, the abdominal pain increased in severity and hematemesis, bloody diarrhea, and gross hematuria were noted. In addition, a tender abdominal mass was detected. Because of this finding, surgical consultation was requested. When first seen by the surgical department the child appeared in acute distress, screaming with paroxysms of abdominal pain to the degree that the initial impression was that the child had experienced an abdominal catastrophe of considerable magnitude. On physical examination, a smooth, tender, grapefruit-sized mass was palpable in the left lower quadrant of the abdomen. In addition, hyperactive bowel sounds were present. Results of a rectal examination were negative, although gross blood was present on the gloved examining finger. Laboratory tests showed a hemoglobin concentration of 10.2 Gm. and a white blood cell count of 17,000 with 62 neutrophils, 28 lymphocytes, and 10 eosinophils. Bleeding time was 2 minutes, coagulation time was 3 minutes and a prothrombin time was 100 per cent of normal. A urinalysis revealed the specimen to be loaded with red cells. Although a roentgenogram of the abdomen showed a few dilated loops of small bowel, the pattern was not consistent with a small bowel obstruction. The abdominal mass was considered to represent a loop of small bowel involved in the pathologic process of Schönlein-Henoch syndrome. The patient was treated conservatively by nasogastric suction, blood and fluid replacement, antibiotic coverage (penicillin, 600,000 U., and streptomycin, 0.5 Gm. daily), and, at the suggestion of the pediatric service, cortisone, 100 mg. daily. Within 12 hours the child's abdominal symptoms were less severe and although the abdominal mass remained essentially the same size, it was less tender. Within 3 days the patient was able to take clear liquids by mouth and the abdominal mass decreased to approximately one-half its original size. In 7 days the mass was no longer palpable and the child was ambulatory and eating a soft diet. Prior to her discharge on the twenty-first day, results of a gastrointestinal series and proctoscopic examination were recorded as normal. A urinalysis showed a microhematuria, but results of a urinalysis 3 months later were recorded as normal.

Comment. The clinical features of Schönlein-Henoch syndrome, as represented by this single case, demonstrate a well-established clinical fact concerning this disease, namely, that Schönlein-Henoch syndrome may simulate a wide variety of acute abdominal surgical conditions. As noted, this child had been subjected to an appendectomy during one attack, and some 16 months later a recurrence presented primarily as an acute small bowel obstruction with an associated tender abdominal mass.

DISCUSSION

Schönlein-Henoch syndrome has been generally recognized as a variant of an allergic reaction. During the last decade, mainly through the accumulation of single case reports in which autopsies have been described and from biopsy study of the

skin lesions, Schönlein-Henoch syndrome has come to be considered a hypersensitivity ity disease on the order of acute glomerulonephritis and polyarteritis nodosa.[7, 9, 10, 14, 20]

One of the first to recognize this aspect of Schönlein-Henoch syndrome was Gairdner[7] who described the microscopic appearance of the skin lesions as a perivasculitis involving the small arteries of the corium. He suggested that this process was responsible for the kidney, joint, and gastrointestinal manifestations and that the purpura simply represented a part of the cellular reaction that accompanied the perivasculitis. He also pointed out the histologic similarity to polyarteritis nodosa, while the renal changes he interpreted as resembling acute and chronic glomerulonephritis. He concluded that each of these conditions was due to the same mechanism, namely, an antigen-antibody inter-reaction that involved the vascular endothelium. In the case of Schönlein-Henoch syndrome, the small arteries of the skin, bowel, and kidney are involved. In periarteritis nodosa, the medium-sized arteries of the body are affected, and in acute glomerulonephritis, the capillaries of the renal glomeruli. Because of the frequency of acute respiratory infections due to beta hemolytic streptococci preceding Schönlein-Henoch syndrome in his group of patients, Gairdner believed a bacterial allergy was the precipitating factor. However, he recognized the factor of food allergy in the initiation of a similar process.[8] The frequency of upper respiratory infection preceding Schönlein-Henoch syndrome has been emphasized by others[7, 9, 14] but the role of a bacterial allergy has been disputed by Ackroyd[1] and Bywaters.[6]

Since Gairdner's publication, a number of authors[9, 10, 12, 14, 20] have reported similar vascular changes, not only in the skin and kidney, but also in the heart, lung, brain, and gastrointestinal tract. The vascular lesions, however, have been most varied, ranging from a nonspecific perivasculitis with only minimal or absent artery wall changes to a necrotizing and proliferative arteritis. To some observers these findings have suggested an immunoallergic reaction.[9] Others, like Lecutier,[10] believe polyarteritis nodosa and Schönlein-Henoch syndrome are the same condition. Vernier,[20] who has studied the renal lesion of Schönlein-Henoch syndrome most extensively, believes that they are comparable to renal changes seen in disseminated lupus erythematosus.

Although there are differences of opinion concerning the etiology and pathogenesis of Schönlein-Henoch syndrome, most authors point out that a perivasculitis is the principal histologic finding. If any conclusions can be drawn from their reports, it would appear that the perivasculitis as it occurs in this disease has a tendency to range over a wide spectrum with respect to the inflammatory reaction and the resulting tissue and vascular injury. At one end of this spectrum the tissue injury is minimal and presumably reversible. At the other end, the tissue injury is severe and is represented by a massive cellular exudation, edema, arterial

Fig. 2. Photograph of the skin rash which shows the purpuric lesions. (From Gairdner, D.: The Schönlein-Henoch Syndrome, Quart. J. Med. 17: 95-123, 1948.)

thrombosis, and infarction. These conditions are complemented by the varied gastrointestinal lesions described at the time of operation, which include edema and hyperemia of the bowel ("not unlike that seen in regional ileitis"[3]), serosal hemorrhage ("like blood injected beneath the serosa"[3]), bowel wall infarction ("like a mesenteric artery occlusion except the mesenteric arteries still pulsate"[4]), gangrene of a loop of bowel, and small bowel intussusception.[3, 5, 19] To most authors, according to Muldoon,[13] the latter event is caused by a segment of involved bowel which interferes with normal peristaltic activity and thus acts as a nidus for the development of an intussusception.

Like the pathologic manifestations, the clinical manifestations of Schönlein-Henoch syndrome are variable and are concerned primarily with the skin, kidney, gastrointestinal tract, and joints. As a rule, symptoms referable to each of the organ systems named may be the first symptom, and not uncommonly they occur in combinations. In most cases, the symptoms are transient and of a short duration, but exacerbations and remissions are frequently observed. Less frequently, the symptoms may be acute and fulminating and deaths have been recorded. Because of these factors, it is difficult to present a concise clinical picture of Schönlein-Henoch syndrome, except to describe in a most general fashion the principal clinical features of the major organs involved.

Briefly, the dermatologic changes of Schönlein-Henoch syndrome may be represented by a purpuric skin rash, urticarial wheels, or simply edema of a localized nature. In its most characteristic form, however, the skin lesion is an erythematous reaction beginning as small, discrete papules which change to a bright pink color in a matter of 2 to 4 hours and later become dull red. Within 24 hours purpura is noted in the form of large irregular patches. In some cases, the lesions may ulcerate and frank gangrene develop. In most instances, the ecchymosis fades away much in the same fashion as common skin bruises, leaving little or no skin residual. According to Gairdner and others,[1, 6, 7] the extensor surfaces of the arms and lower extremities are the common sites of involvement.

The joint symptoms consist mainly of pain and swelling of the ankle and knees. The arthralgia is usually not severe when compared to the joint pain of rheumatic fever, while the swelling appears in many cases to be periarticular rather than intra-articular. The chief renal symptom is gross hematuria. Of greater significance is the fact that the renal sequelae of Schönlein-Henoch syndrome may resemble a chronic nephritis-like clinical pattern.[11, 20, 21]

The visceral manifestations of Schönlein-Henoch syndrome are likewise quite variable, particularly in the degree of their intensity. The predominating gastrointestinal symptoms are crampy abdominal pain, vomiting, diarrhea, gastrointestinal bleeding, and, occasionally, an acute abdominal mass. In some instances, the symptoms may develop to the point of suggesting an acute abdominal condition and in the surgical literature there are a number of well-documented cases in which an exploratory laparotomy has been performed.[3, 4, 6] In the majority of these cases the preoperative diagnosis was either acute appendicitis or small bowel obstruction. Besides the ability of Schönlein-Henoch syndrome to mimic an acute abdominal condition, it has been well established that the disease itself can result in complications that require surgical treatment. These include bowel wall infarction and intussusception.[3-5, 13]

Because of the surgical implications a review was made of cases available in the literature in which surgical intervention was deemed necessary. It was observed that the two most common problem cases relegated to the surgeon were (1) those of Schönlein-Henoch syndrome in which the abdominal manifestations ushered in the diseases without the benefit of the skin and joint changes and in which the clinical course suggested an acute appendicitis, and (2) those in which small bowel obstructive symptoms and/or a painful abdominal mass was the principal problem. In most of the latter

cases the diagnosis of Schönlein-Henoch syndrome was already established prior to operation.

In an evaluation of the two problem groups, it would appear that in the former one must assume that, if there is reasonable doubt, an exploratory laparotomy is preferable to missing the diagnosis of an acute appendicitis. Suffice it to say, there is no specific laboratory test that permits one to make even a presumptive diagnosis of Schönlein-Henoch syndrome under such conditions. In the latter group, when the presence of an acute gastrointestinal mass is the principal problem, it would seem reasonable to evaluate such cases according to the general surgical principles which concern any acute abdominal mass, namely, to determine from the clinical examination whether reversible or irreversible tissue injury has taken place and to plan the operation accordingly, with the understanding that the underlying process in Schönlein-Henoch syndrome is a perivasculitis and that much of the early tissue change is a result of the associated cellular exudate that includes all of the cellular elements, even red blood cells. When such an event takes place within the confines of the bowel wall, the number of possibilities become apparent and each is dependent on the intensity of the perivasculitis and the host response. As a point of interest, Steinhardt,[19] in a review of the world literature in 1955, was able to document 24 cases of Schönlein-Henoch syndrome complicated by a small bowel intussusception. From the author's review of the surgical literature, it was found that gangrene of a loop of bowel in this condition is even less common.[13, 14] The latter finding suggests that the surgical complications resulting from the perivasculitis of Schönlein-Henoch syndrome are rare and that conservative measures should be employed unless signs and symptoms of impending peritonitis or bowel obstruction due to intussusception are most specific.

The treatment of Schönlein-Henoch syndrome is primarily supportive with emphasis directed to the control of pain and maintenance of nutritional and fluid requirements by parenteral therapy. In recent years, a number of reports[2, 17, 18] have advocated the use of corticosteroids. Their beneficial effects, however, are controversial. As indicated previously, the etiologic role of bacterial infections and principally those due to the beta hemolytic streptococcus is inconclusive. There appears to be a bacterial interrelationship in this disease that suggests that foci of infection be determined and treated by the appropriate antibiotic.

SUMMARY

Five cases of Schönlein-Henoch syndrome in children have been presented and their surgical implications emphasized. The surgical features of this disease are concerned primarily with the gastrointestinal tract in that a surgical emergency may be simulated, and less commonly the disease process itself may result in serious gastrointestinal complications, most often small bowel intussusception. The cause of these conditions is a perivasculitis and its associated cellular extravasation. The exact etiology of this disease is indeterminate.

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Further observations on the use of I^{131}-labeled triolein in the diagnosis of chronic relapsing pancreatitis

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At times chronic relapsing pancreatitis presents a characteristic clinical picture and may be easily diagnosed. In the advanced stage there are deficiencies in both endocrine and exocrine secretions which cause abnormal results of pancreatic function tests or gross steatorrhea. However, in the uncomplicated case without sequelae most, if not all, results of the usual tests will be normal and diagnosis may be difficult, if not impossible, without exploratory laparotomy.

Earlier reports[6, 7] from this institution concerning a small group of patients with pancreatitis indicated that I^{131}-labeled triolein was a useful diagnostic tool, for 10 of 12 patients had abnormal blood values. Additional experience with a larger group of patients indicates that abnormal values usually are obtained only when the disease is advanced and that there are many patients who have proved chronic pancreatitis with normal fat absorption as reflected by the I^{131}-labeled triolein test.

The purpose of this report is to compare the results of the test in patients without complications with the results in those with the usual sequelae, that is, calcification, diabetes, or gross steatorrhea, and in particular to appraise the usefulness of the test in the diagnosis of chronic pancreatitis.

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METHOD

The I^{131}-labeled triolein test was conducted in a manner previously described.[1] The diagnosis of pancreatitis was established by operation or by a typical clinical history plus either pancreatic calcification or an amylase greater than 500 Somogyi units on one or more occasions.

RESULTS

The results of the average hourly determinations of blood levels of radioactivity and fecal excretion of I^{131}-labeled triolein in patients with pancreatitis without sequelae are presented in Table I. Of the 17 patients studied, only 2 had consistently abnormal blood levels and 6 patients had at least 1 abnormal fecal level of radioactivity. There were 7 patients (41 per cent) with either an abnormal blood or fecal level or both (Table II).

Table III gives results of determinations of blood and fecal levels of radioactivity in 18 patients with sequelae. Ten patients had abnormal blood levels and 7 of the 10 patients from whom stool collections were available had an abnormal fecal level of radioactivity. There were 13 patients (72 per cent) who had either an abnormal stool or blood level or both (Table IV).

It should be noted that of the various sequelae, calcification was most often associated with an abnormal result. In fact, only 3 of the 10 patients with calcification had normal results. In 2 of these, only blood values were available.

Table I. *Patients without sequelae*

Patient No.	*Date of test*	*Blood levels of radioactivity**	*Fecal level of radioactivity† (%)*
1	Dec. 30, 1957	9.7	No specimen
	Jan. 14, 1958	14.4	2.0
2	Feb. 5, 1958	6.8‡	6.0‡
	Feb. 7, 1958	6.8 (oleic)	7.0 (oleic)
	Oct. 14, 1959	2.4	33.0
3	Aug. 26, 1955	13.4	0.5
4	Oct. 20, 1954	20.8	No specimen
5	July 8, 1957	6.8	No specimen
	Sept. 25, 1957	10.5	No specimen
	Sept. 18, 1958	10.3	No specimen
6	Oct. 29, 1956	11.3	No specimen
7	Feb. 25, 1958	14.5	0.1
	Feb. 28, 1958	14.9 (oleic)	1.0 (oleic)
	June 2, 1959	16.4	1.0
	June 16, 1959	15.8	2.01
8	Nov. 16, 1954	9.9	No specimen
	May 3, 1956	10.4	13.8‡
	April 28, 1958	10.5	0.2
9	March 15, 1956	4.9‡	16.5‡
10	Jan. 4, 1956	11.3	No specimen
11	Sept. 8, 1958	11.3	No specimen
12	Aug. 9, 1957	14.6	No specimen
13	Oct. 14, 1957	18.1	0.1
14	March 24, 1958	8.8	10.1‡
	March 31, 1958	9.3	1.3
15	May 27, 1957	19.0	0.14
	Oct. 10, 1958	13.0	0.70
	May 19, 1959	15.5	1.0
16	Oct. 24, 1956	8.6	7.0‡
	Dec. 26, 1956	8.1	30.0
	Nov. 20, 1958	6.8	2.4
17	Dec. 5, 1957	10.0	25.0‡

*Average of fourth, fifth, and sixth hour samples.

†Forty-eight hour stool collection.

‡Abnormal levels.

Two or more tests were performed on a total of 11 patients in both groups. Although there was a wide range of values, the reproducibility of the results in the same patient is to be emphasized. Multiple tests in the same patient usually gave either high or low blood levels of radioactivity and reciprocal depression or elevation of fecal values. In general, with periods of observation ranging up to 3 years, there was little change in the individual patient's absorption of I^{131}-labeled triolein. At times, an isolated normal fecal value was noted in spite of low blood levels of radioactivity. This is probably best explained on the basis of incomplete stool collection.

The average blood levels of radioactivity and the average fecal excretions of I^{131}-labeled triolein in both groups are shown in Fig. 1. In patients with no sequelae, the average blood level of radioactivity was 11.4 per cent and the average fecal value was 8.1 per cent, the latter being abnormal. In the patients with sequelae, the average blood level was 7 per cent and the average fecal excretion was 21.6 per cent. The difference between the results in the two groups is ap-

Table II. *Seventeen patients without sequelae*

	Normal	*Abnormal*
Blood values	15	2
Fecal values	5	6
Blood and fecal values	10	7

parent (blood, p equals less than 0.01; fecal, p equals less than 0.05, greater than 0.01).

Absorption of I^{131}-labeled oleic acid was measured in a total of 7 patients in both groups. In 5 cases the blood level of radioactivity after administration of oleic acid was markedly above the level after triolein administration. In 4 patients with stool examinations, the results in 2 were significantly lower after administration of oleic acid than after triolein administration. In the other 2 patients fecal values were normal after administration of both oleic acid and triolein.

DISCUSSION

It was hoped that the I^{131}-labeled triolein test would prove useful in the diagnosis of obscure cases of chronic relapsing pancreatitis. Early observations suggested that the test was of value, for it pointed to the correct diagnosis in 10 of 12 cases. Further experience with the procedure has been disappointing. In patients with advanced disease and complication, especially when calcification is present, the test results are usually positive. However, in patients with the early stage of the disease without sequelae, the test re-

Table III. *Patients with sequelae*

Patient No.	*Date of test*	*Complication**	*Blood levels of radioactivity†*	*Fecal level of radioactivity‡ (%)*
1	Aug. 10, 1955	C	6.8	No specimen
2	Oct. 22, 1956	C	14.8	No specimen
3	Oct. 7, 1957	C	19.3	0.63
	Oct. 10, 1957	C	17.2	0.52
4	Nov. 29, 1954	C, D	0.7§	0.6
	March 25, 1958	C, D	2.4	No specimen
5	Oct. 12, 1958	C, D	9.5	12.0§
	Nov. 22, 1958	C, D	12.9 (oleic)	No specimen (oleic)
	Dec. 2, 1958	C, D	6.8	40.0§
	Jan. 12, 1959	C, D	9.3	9.4§
	April 10, 1959	C, D	7.3	No specimen
6	Aug. 31, 1956	C, D, S	12.6	6.0§
	Dec. 29, 1958	C, D, S	4.9§	36.0§
	Nov. 24, 1958	C, D, S	11.4 (oleic)	No specimen
	Nov. 19, 1958	C, D, S	7.1	36.0§
	Jan. 3, 1959	C, D, S	10.9 (oleic)	11.8 (oleic)
	Sept. 22, 1959	C, D, S	6.7§	18.8§
7	March 3, 1958	C	3.0§	0.32
	Sept. 16, 1958	C	4.4§	19.0§
	Dec. 11, 1958	C	2.6§	14.6§
	Sept. 10, 1959		3.01§	14.1§
8	Sept. 30, 1957	C, S	3.7§	20.6§
	Oct. 7, 1959	C, S	3.8§	1.3
	Oct. 11, 1957	C, S	1.6§	60.9§
	Jan. 16, 1958	C, S	11.3 (oleic)	No specimen
9	Aug. 24, 1955	C, S	0.8§	57.3§
10	Sept. 2, 1955	C	6.8§	No specimen
11	Jan. 10, 1956	C	9.7	No specimen
12	Jan. 23, 1960	D, S	0.6§	No specimen
13	Feb. 4, 1957	D	13.0	No specimen
14	Dec. 29, 1958	D	6.4§	3.3
	Jan. 6, 1959	D	12.4 (oleic)	1.4 (oleic)
15	Nov. 27, 1956	D	1.5§	No specimen
	Nov. 30, 1956	D	4.0 (oleic)	No specimen (oleic)
16	Sept. 1, 1959	S	12.7	11.18§
17	May 16, 1958	S	8.5	30.9§
18	Sept. 2, 1955	S	10.6	No specimen

*C, calcification, D, diabetes, S, steatorrhea.

†Average of fourth, fifth, and sixth hour samples.

‡Forty-eight hour stool collection.

§Abnormal levels.

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Table IV. *Eighteen patients with sequelae*

	Normal	*Abnormal*
Blood values	8	10
Fecal values	3	7
Blood and fecal values	5	13

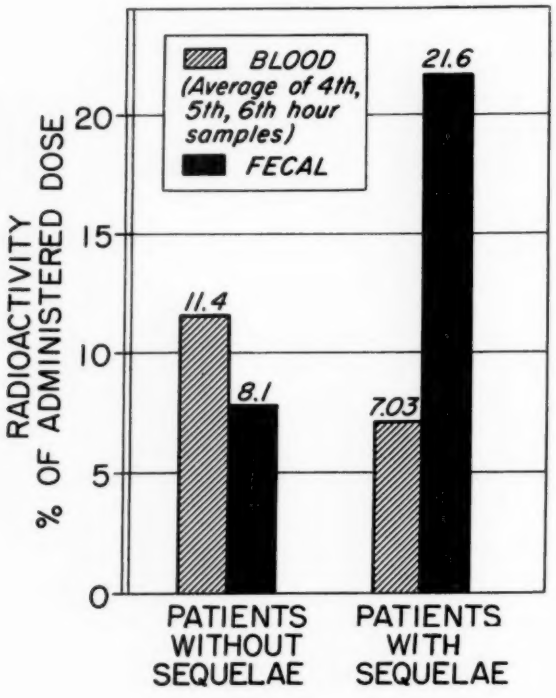

Fig. 1

sults are often normal. Since the test is merely a reflection of pancreatic insufficiency, this is not surprising.

Similar results with I^{131}-labeled triolein have been reported by Polachek and associates,[5] who found an essentially normal mean plasma level of radioactivity in 8 patients without sequelae, but the average of the fecal excretions was elevated in the 4 such cases reported. In their patients with calcification both the average blood and average fecal values were abnormal.

The differences in the results of the triolein test in our two groups of patients are confirmed by observations of Dornberger and associates,[2] who reported fat balance studies in a group of patients with pancreatitis. Only 1 of 10 patients with pancreatitis and no sequelae had an abnormal fecal fat value, whereas 10 patients who had calcification with or without diabetes or gross steatorrhea as determined on a clinical basis alone were all found to have elevated fecal fat levels. However, in 3 of these patients the fecal fat level was only slightly elevated (7.7, 8.1, and 8.3 Gm., respectively), while they were on a diet of 101.6 Gm. of fat.

Thus it would appear that results of both the triolein test and fecal fat test, chemically determined, are apt to be normal in the obscure, difficult case and likely to be abnormal in the patient with advanced disease in whom the diagnosis has already been suspected, if not established. In our experience, the triolein test is far more valuable in the diagnosis of carcinoma of the pancreas, as 41 of 51 patients (80 per cent) have had a positive result.[4] We have also found the test useful in the evaluation of the effect of treatment, both after replacement therapy and after definitive surgery such as caudal drainage or sphincterotomy.[3]

SUMMARY

1. I^{131}-labeled triolein tests have been performed in 35 patients with chronic relapsing pancreatitis.

2. In the group without sequelae, the test was helpful in approximately one-third of the cases only.

3. As expected, in patients with sequelae the results were generally abnormal.

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Meckel's diverticulum associated with carcinoid tumor

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Carcinoid tumor occurring in a Meckel's diverticulum is an unusual finding. Because the incidence of Meckel's diverticulum is only 0.2 to 3 per cent and carcinoids are relatively rare gastrointestinal lesions, the probability of their occurring together is correspondingly low. To date, 15 cases have been reported.[1-6, 8-16] Therefore it is not possible to draw any conclusions concerning clinical significance and it is our opinion that more reports of these interesting occurrences are needed.

The earliest case report (1922), by Hicks and Kadinsky,[3] was challenged by Stewart and Taylor[14] who believed the lesion to be ectopic gastric mucosa. In the 16 cases available, including the one of Hicks and Kadinsky and the present one, all the lesions occurred in males except the one reported by Price.[12] The patients ranged in age from 12 to 68 years with a mean of 50.6 years. In 4 lesions there was evidence of inflammation. The rest were removed incidentally at operation or autopsy. Most were smaller than 1 cm. in diameter; the largest was 2.0 cm. Only in the case reported by Stoll[15] were there distant metastases (0.6 per cent) while 3 lesions (18.7 per cent) had infiltrated the muscularis mucosa.

CASE REPORT

On May 27, 1960, a 64-year-old white man underwent cholecystectomy and exploration of the common duct with transduodenal sphincterotomy for cholelithiasis and stenosis of the sphincter of Oddi. On abdominal exploration a 2 by 5 cm. diverticulum of the ileum was found 44 cm. above the ileocecal valve. It was operated and a submucosal nodule measuring 10 by 7.5 mm., pale yellow in color and well demarcated, was present in the submucosa near the tip. It was not ulcerated and was thought to represent ectopic pancreas. No lymph nodes were enlarged and the liver was normal.

Microscopic examination showed a typical carcinoid tumor (Fig. 1). No mitotic figures were seen. The mucosa was intact. This neoplasm was made up of well-defined nests of cells with an organoid appearance. It was demarcated, involved the tunica propria, and extended deep into the muscular wall. Silver reaction as described by Masson[7] was positive (Fig. 2).

The patient himself gave no history of weight loss, diarrhea, or intestinal obstruction. Blood pressure was 120/80 mm. Hg and the heart was normal on physical examination. No flushing, cyanosis, or bronchoconstriction had been noted.

Multiple qualitative tests for 5-hydroxyindoleacetic acid were performed on the patient's urine, all of which gave negative results. Serum sodium and fasting blood sugar determinations were within normal limits.

DISCUSSION

The low rate of metastases seen to date with carcinoids which occur in a diverticulum is comparable to that found with carcinoids in the appendix. Only some 25 malignant appendiceal carcinoids have been reported in the literature. In 25 such cases collected from 5 hospitals in Nashville[17] there was only 1 in which the lesion had extended into the appendiceal mesentery and no distant spread was evident. It is interesting to

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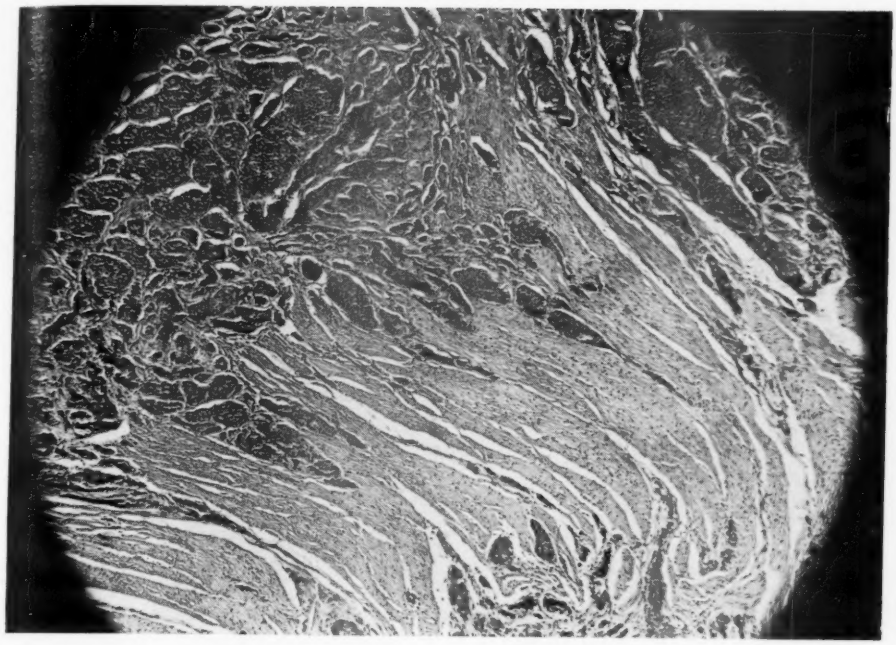

Fig. 1. Carcinoid tumor involving the muscularis externa of Meckel's diverticulum. (Hematoxylin and eosin; ×60; reduced ⅓.)

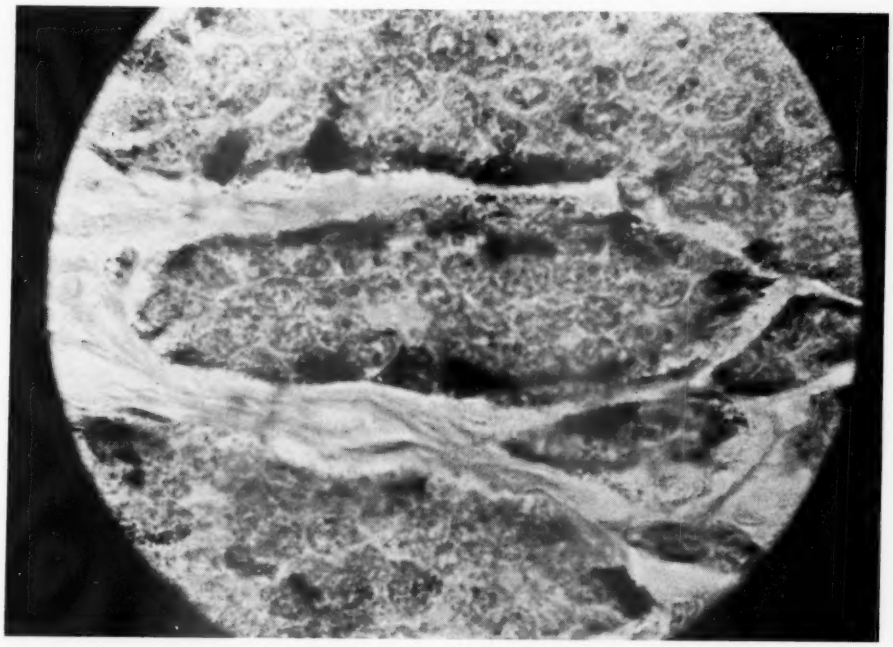

Fig. 2. Carcinoid tumor with argentaffin granules. (Masson's trichrome; ×950; reduced ⅓.)

speculate on why carcinoids which occur out of the main stream of the gastrointestinal tract should be more benign in their characteristics than those of the stomach or small or large bowel. It has frequently been stated that appendiceal carcinoids cause luminal obstruction earlier than those in other locations and therefore, being slow-growing tumors, are removed before they have a chance to metastasize. Only 4 of the 16 patients whose cases are reviewed here had diverticulectomy for inflammatory dis-

ease and it seems unlikely that a carcinoid of the size found would lead to this inflammation. It may be that carcinoids of Meckel's diverticula and appendix have a lower potential of malignancy and are actually more benign than those occurring elsewhere. When a greater number of such cases are available, perhaps this point will be more clearly defined.

SUMMARY

Of the 15 cases of Meckel's diverticulum associated with carcinoid tumor reported to the present time, 7 were discovered at autopsy, 7 occurred in conjunction with diverticulitis, and 4 were found incidentally at operation. One had distant metastases and 2 had invaded the muscularis mucosa. In our case, the sixteenth to be reported, the lesion was an incidental finding at operation for cholecystectomy and sphincterotomy. No distant metastases were evident but the muscularis mucosa was infiltrated. Results of 5-hydroxyindoleacetic acid determinations were negative and no signs or symptoms of the malignant carcinoid syndrome were present.

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Meckel's diverticulum: an unusual position

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The aggravating knack of the diverticulum of Meckel for evading *preoperative* diagnosis is well known. It is not called the "abdominal masquerader" in jest. Its occurrence in 2 per cent of all persons (which makes it the most frequent malformation of the gastrointestinal tract) in no way pacifies the diagnostician. This report concerns its less-known ability to evade *operative* diagnosis, an aspect which has come to our attention because of an apparently unique position of a Meckel's diverticulum in a recently treated patient.

It is usually stated that Meckel's diverticulum is invariably found on the antimesenteric border of the bowel. This location is of twofold significance. First, it is in keeping with the embryologic derivation. Second, it is of clinical import because in the common practice of examining the distal 2 to 5 feet of ileum for a Meckel's diverticulum (whether or not it is primarily suspect), the surgeon often does not carefully inspect the mesenteric border. A small diverticulum may pass unnoticed if it lies within or against the mesentery unless it is specifically sought out in this position. Indeed, Potts[5] mentions a case in point: "A four-year-old boy had had a couple of episodes of brisk rectal bleeding. At operation, at a hospital ordinarily referred to as 'elsewhere,' no diverticulum had been found. Bleeding persisted. At a second operation a diverticulum was found in the mesentery of the bowel, covered with adhesions. It looked and felt like a large lymph node." It had been of an antimesenteric origin, but was plastered to the mesentery.

Thus mention is often made of the fact that although a Meckel's diverticulum originates from the antimesenteric border, it may swing over against the bowel to lie on the mesentery, where adhesions secondary to peptic ulcer may secure it firmly, and casual inspection will show only an apparently normal ileum. I have been unable to find a report of a Meckel's diverticulum originating from the mesenteric border. The following case illustrates this occurrence.

CASE REPORT

M. S. D., a 6-year-old white male, was admitted to the surgical service of the 3610th USAF Hospital, Harlingen Air Force Base, at 5 A.M. on March 8, 1960, with severe generalized abdominal pain which had started at midnight. After the onset of pain he had been given an enema by his mother with good fecal return, but with subsequent rather forceful vomiting of blood-streaked liquid and an increase in pain. The youngster lay quietly in bed in moderate distress from abdominal pain. The abdomen was flat with hypoactive peristalsis of normal pitch. There was moderate generalized rigidity and tenderness, most marked in the right lower quadrant. The white blood count was 16,200 with 90 per cent polymorphonuclear neutrophils.

The initial diagnosis was acute appendicitis with perforation. At laparotomy, 200 to 300 ml. of milky liquid was found in the peritoneal cavity. The appendix was retrocecal and apparently indurated. Only after excision did it become clear that it was normal. The true source of the peritonitis was then identified. There was a perforation 4 mm. in diameter on the mesenteric aspect of the terminal ileum approximately 2 feet from the ileocecal junction. No diverticulum was apparent. There was an inflammatory mass 3 to 4 cm. in diameter in the mesentery immediately adjacent to the perforation which was

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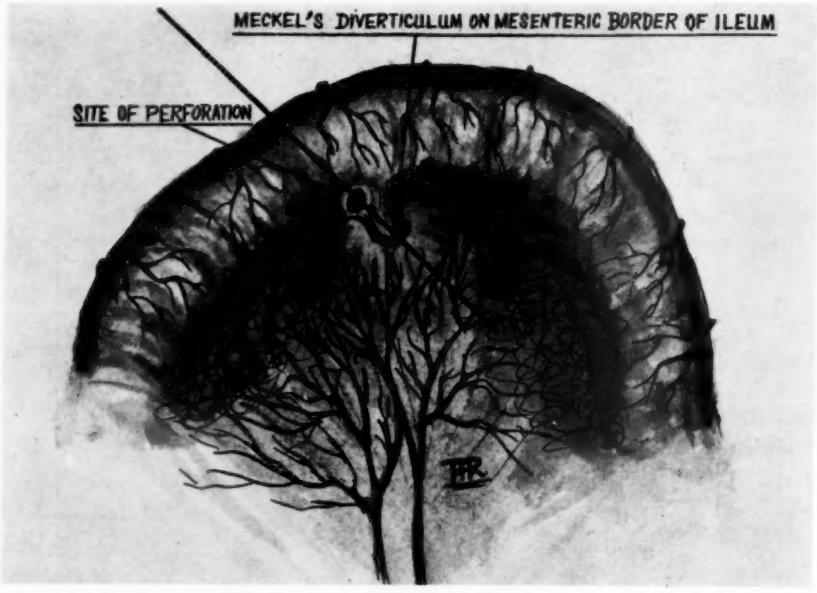

Fig. 1. Meckel's diverticulum on mesenteric aspect of ileum with perforation at base.

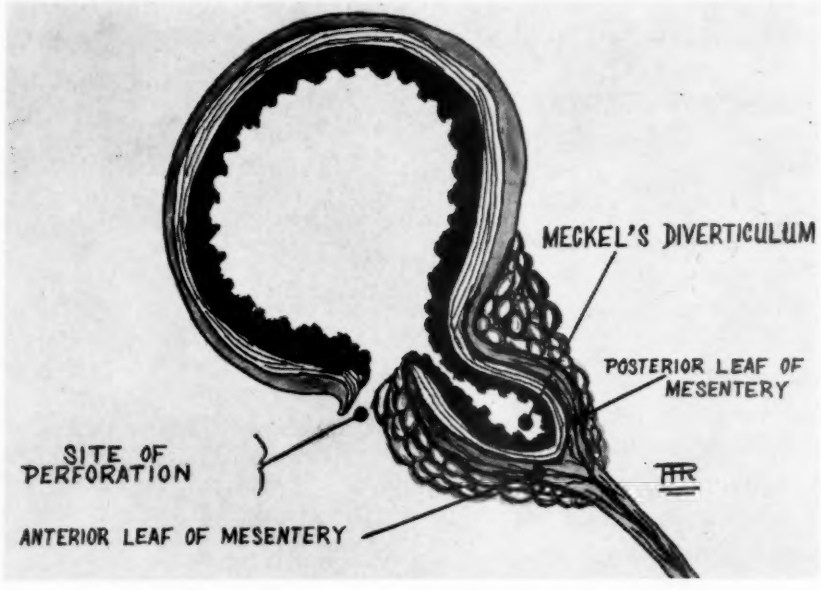

Fig. 2. Cross section of ileum (at level indicated by heavy line in Fig. 1), which demonstrates location of diverticulum within mesentery.

thought to be a lymph node. A resection of the involved segment of ileum was performed with end-to-end anastomosis.

The patient's postoperative course was smooth and he was discharged 1 week postoperatively.

Dissection of the specimen showed that what had appeared to be an inflammatory mass at operation was actually a 14 by 14 mm. Meckel's diverticulum which opened quite definitely on the mesenteric side of the ileum (Fig. 1). The diverticulum was lined by gastric and ileal mucosa and had a perforation at its neck. The antimesenteric border was as normal as it had appeared in the operating room. Microscopically the diverticulum was covered on one lateral surface by mesenteric fat and on the other surface by fat which could have been either mesenteric or omental. Since there were no omental adhesions found at operation, however, the latter surface probably was covered by mesenteric fat also, with

the diverticulum lying within the mesentery rather than against it (Fig. 2). There was no doubt about the mesenteric location of its mouth.

SUMMARY AND CONCLUSIONS

It is easy to miss a 1 cm. long Meckel's diverticulum which lies within or against the mesentery rather than in its usual antimesenteric position. It may have swung into the mesenteric position from an antimesenteric origin, or it may have arisen from the mesenteric border. The mesentery thus aids in the masquerade. A search for this lesion without careful examination of the mesenteric border of the small bowel is incomplete.

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Veno-occlusive disease of the liver: surgical aspects

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Veno-occlusive disease of the liver was established as a disease entity only a few years go and has not yet been included in the surgical literature as a cause of portal hypertension. Although cirrhosis of the liver had previously been noted in Jamaican children,[35, 47] the pathogenesis and pathology were not defined until 1954.[9, 27, 53] Since then it has been found to occur in other parts of the Caribbean[55] and sporadically in Africa.[49] The cirrhosis seen in Indian children has some features in common but differs from veno-occlusive disease in other respects.[26]

It is the purpose of this communication to provide a brief review of the disease but more particularly to discuss its surgical implications. The discussion will be based on the 99 histologically authenticated cases of this disease so far seen at the University College Hospital of the West Indies.

At the present time the disease is thought to be due to the action of certain plant toxins. Senecio and Crotalaria have been singled out for suspicion as they are frequently used in the form of herbal infusions either as beverages or medicines by peasants in Jamaica, while *Crotalaria fulva* has been found to reproduce the syndrome of veno-occlusive disease in experimental animals.[7] Veno-occlusive disease is the commonest cause of cirrhosis of the liver in Jamaican children and accounts for 30 per cent of all cases of cirrhosis in patients of all ages.

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The target area appears to be the centrilobular parenchymal cells of the liver and the intrahepatic radicles of the hepatic veins.

PATHOLOGIC CHANGES

In the acute stage there is a blockade of the small hepatic veins. The medium-sized veins are somewhat affected and the larger veins are essentially spared. The nature of the block has been discussed in detail in earlier publications,[8, 9] but essentially it consists of an acute exudative subendothelial intimal thickening with partial or complete occlusion of lumen (Fig. 1). Concomitant with the block is a marked congestion in the centrilobular areas of the liver and varying degrees of necrosis of parenchymal cells, again in the center of the lobules (Fig. 2).

In patients who recover from the acute stage the centrilobular congestion subsides. Collateral vessels through distended sinusoids, which form new pathways but bypass the blocked vessels, remedy the circulatory disturbance in the center of the lobule. In these patients there is no permanent damage and in biopsies taken up to 3 years after a single acute episode there has been no residual fibrosis in the liver.

Interestingly enough, there is no other vein in the body which is affected in a similar way. The lesion is exclusively located in the hepatic veins.

The subacute stage is characterized histologically by persistent fibrosis in the centrilobular (nonportal) area. Here recurrent

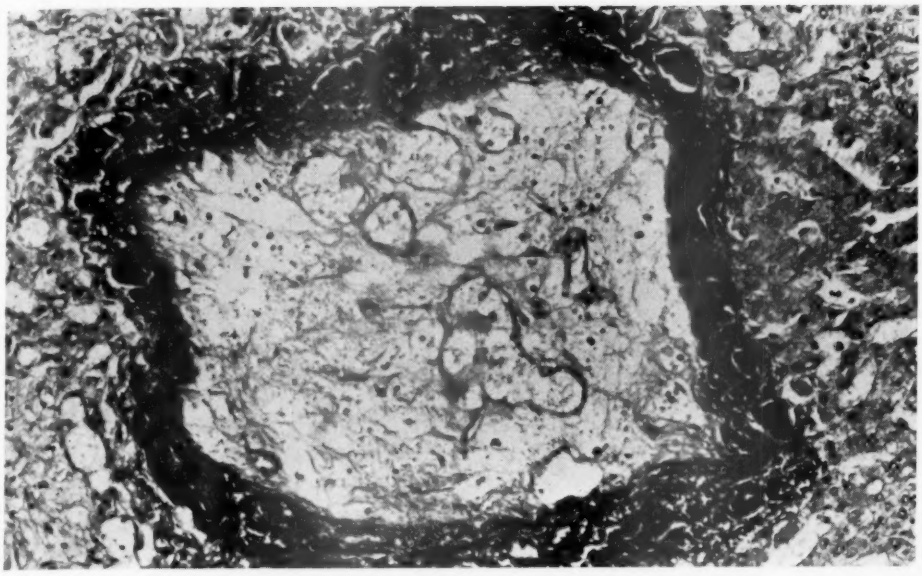

Fig. 1. Acute veno-occlusive disease of the liver. Exudative subendothelial thickening with almost complete obliteration of lumen of hepatic vein.

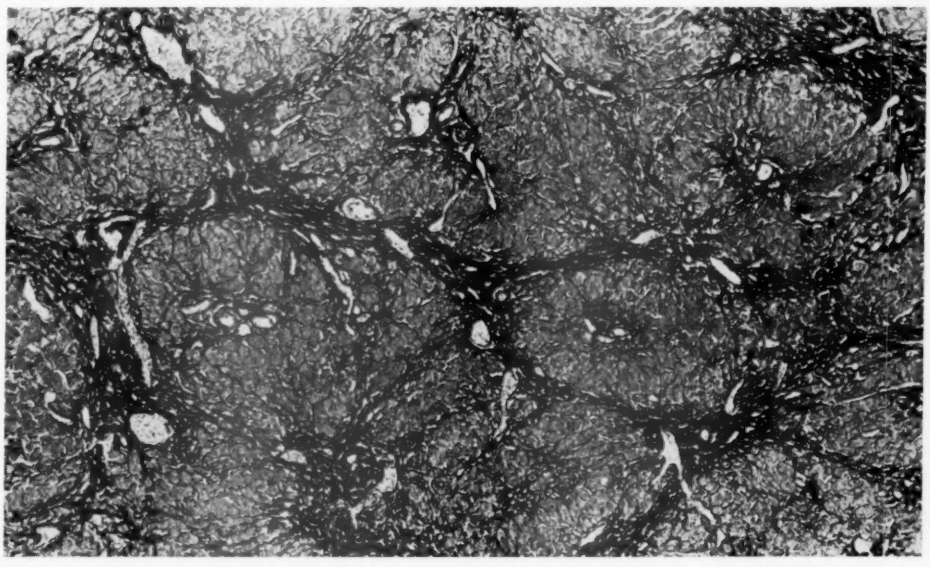

Fig. 2. Veno-occlusive disease of the liver. Centrilobular congestion and fibrosis.

episodes of blockage of the centrilobular veins leave these vessels with thickened walls while the centrilobular parenchymal necrosis is followed by deposition of fibrous tissue.

The chronic stage is one of nonportal cirrhosis, clinically indistinguishable from any other type of cirrhosis (Figs. 3 and 4). Our morphologic studies indicate that this is the result of repeated veno-occlusion with subsequent irreparable damage to the nonportal areas, scarring, formation of collateral circulation, and nodular regeneration.

CLINICAL FEATURES

The clinical picture produced resembles the Budd-Chiari syndrome, for which the disease was originally mistaken.

It may occur in patients of any age and in either sex. It has been seen here in pa-

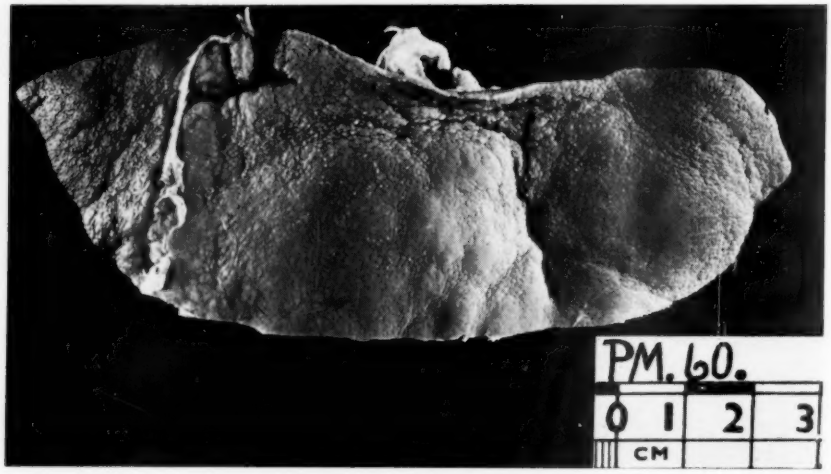

Fig. 3. Chronic veno-occlusive disease of the liver.

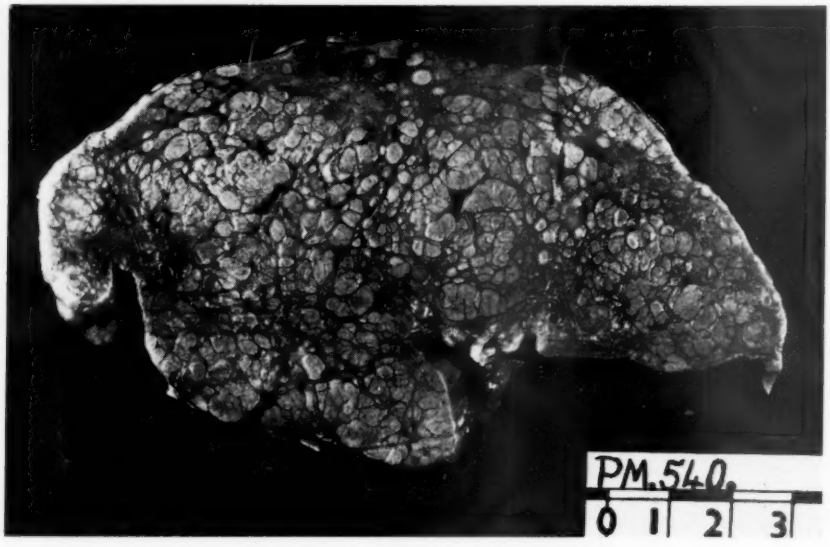

Fig. 4. Chronic veno-occlusive disease of the liver.

tients as young as 3 months and as old as 52 years. However, the peak incidence is in patients between 2 and 5 years of age. Seventy-six per cent of our patients were under 10 years of age and 90 per cent under the age of 20. Mortality rate is highest at both extremes of life, being 32 per cent in infants and 58 per cent in adults. On a comparative basis, more adults die in the acute phase, while more children die in the chronic phase (Fig. 5).

In at least 73 per cent of our patients, there has been a prodromal stage resembling either an upper respiratory infection with cough and fever or, less commonly, a gastrointestinal upset with nausea, vomiting, diarrhea, and fever. This is followed within 1 or 2 weeks by the abrupt onset of ascites in all instances and a moderate to marked fever. There may be jaundice (30 per cent), edema of the feet (33 per cent), or, less often, of the hands and face as well, and hepatosplenomegaly. Pleural effusion, usually of the right side, may be present (27 per cent). In more severe cases anorexia and lethargy are noted.

Liver function tests made during this stage show evidence of mild to marked hepatocellular damage and a more favorable prognosis is often but not invariably

associated with the milder changes. It has been found[54] that in the acute phase of veno-occlusive disease, the levels of the serum albumin and cholinesterase on admission provide a good guide for assessing prognosis. There is also quite frequently, however, an elevation of the alkaline phosphatase level and prolongation of the prothrombin time, and the present study would indicate that these often presage gastrointestinal bleeding. Thus, in 14 of such patients studied, all bled from esophageal varices, and the average level of the alkaline phosphatase was 21 King-Armstrong units (range 12 to 33) and the average prothrombin time was 18 seconds (range 14 to 25). During the acute phase the color of the urine and stool is rarely if ever altered.

Sixteen per cent of our patients have died in the acute phase, after an illness lasting from 7 days to 4 months. Death has most often been due to liver failure, although in 5 instances it was caused by bleeding from ruptured esophageal varices and 4 patients died from other causes (Table I).

Twenty-three per cent of our patients, however, have made a clinical recovery in 4 to 6 weeks and have remained asymptomatic. This has been documented by serial liver biopsies when possible or by reversal to normal of the results of liver function tests. The ascites and hepatomegaly often receded as rapidly as they had started and the shorter the duration of these, the better the prognosis has been. Care in the hospital usually has been only supportive.

Seventeen per cent of our patients have passed into the chronic phase and then died of their disease after an illness of approximately 28 months. Seventeen per cent have been lost to follow-up. In 26 per cent the disease has progressed into the chronic phase and follow-up has been continued, in some instances for over 5 years (Table II). This phase is characterized by continued hepatosplenomegaly and the establishment of a cirrhosis which, if seen microscopically for the first time at this stage, cannot always be distinguished in the biopsy from other types of cirrhosis. Approximately 18

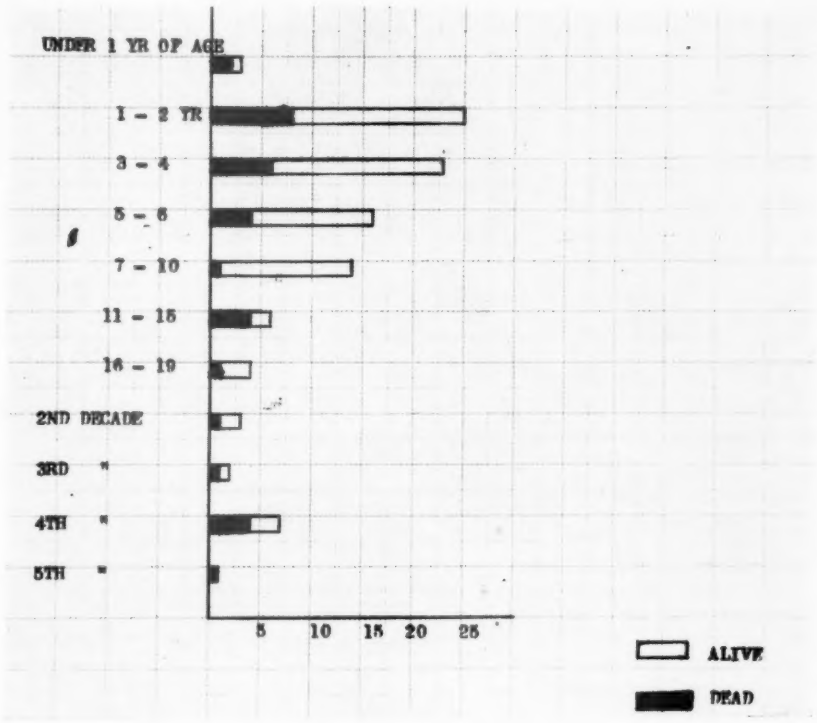

Fig. 5. Age incidence and mortality rate of patients with veno-occlusive disease of the liver.

Table I. *Veno-occlusive disease of the liver: natural history*

% of 99 patients	*Outcome*
16	Died in acute phase
23	Made complete clinical recovery
17	Died in chronic phase
26	Alive with cirrhosis
17	Lost to follow-up

per cent of our patients at this stage have exhibited dilated abdominal veins not infrequently associated with a continuous venous hum which is usually loudest at the xiphisternum. The onset of cirrhosis is more rapid than that from other causes and has been documented as early as 3 months after the onset of the acute lesion.

There have been 33 deaths and a postmortem rate of 87.8 per cent. In the acute phase death has most often been due to progressive liver failure (10 of 12 cases), while in the chronic phase most deaths (12 of 17 cases) have been due to ruptured esophageal varices. Four patients died of unrelated causes (Table III).

In all, 17 patients have died of esophageal hemorrhage, 5 during the acute phase of veno-occlusive disease and 12 during the chronic phase. Thirteen of these patients died during the first bleeding episode, 3 during the second bleeding episode, and 1 during the fourth episode. It is a remarkable fact that of 8 patients admitted with concomitant epistaxis, 5 subsequently died of ruptured varices during that admission. As we have studied only 15 patients completely by esophagram or esophagoscopy, the true incidence of esophageal varices in veno-occlusive disease is probably considerably higher than the 23 per cent indicated in Table IV. Because of errors in interpretation, we now prefer to rely on esophagoscopy rather than esophagram for the demonstration of varices in children. It will also be noted that of 29 patients with gastrointestinal bleeding 17 died of esophageal hemorrhage (Table V).

The patient, then, with chronic veno-occlusive disease of the liver who develops portal hypertension as evidenced by esophageal varices has an extremely poor prognosis. In an effort to salvage this group it was decided to offer portacaval shunting even if overt bleeding had not yet occurred. In the past 2 years of this program 4 patients have been selected for operation. All survived operation and have done well clinically since. It has been possible to follow all of them closely and at regular intervals.

CASE REPORTS

Case 1. S. J., a 7-year-old girl, was admitted on March 24, 1958, because of progressive ascites and enlarging esophageal varices.

She had been first seen in March, 1953, at the age of 1 year, 8 months, when she was admitted because of acute veno-occlusive disease. There was a 3-week history of cough and fever followed by anorexia, vomiting, and abdominal discomfort and swelling of 4 days' duration. Diet had been poor and supplemented by "bush teas." She remained afebrile in the hospital, did not have jaundice or pedal edema, but had hepatosplenomegaly. Needle biopsies of the liver confirmed the diagnosis of acute veno-occlusive disease of the liver. The ascites was tapped, the liver became smaller, and she was discharged on May 9, 1953.

On readmission in February, 1954, liver biopsy again demonstrated marked veno-occlusive disease (subacute type).

Table II. *Follow-up data*

Clinical status	*Duration of follow-up (years)*						*Total*
	Under 1	*1-2*	*2-3*	*3-4*	*4-5*	*Over 5*	
Dead	—	—	—	—	—	—	33
Untraced	—	—	—	—	—	—	17
Chronic (cirrhosis)	14	7	—	1	2	2	26
Asymptomatic	7	5	1	4	2	4	23
Totals	21	12	1	5	4	6	99

She was admitted for a third time in May, 1958, because of vomiting and recurrent ascites. Repeated paracenteses were carried out and barium studies demonstrated increasing varices in the lower third of the esophagus. Repeat liver biopsies showed increasing centrilobular fibrosis with congestion and widening of the sinusoids. The child was anemic but stools did not contain blood. It was believed the veno-occlusive disease had progressed to the chronic stage with portal hypertension. She was prepared for portacaval shunt and on June 23, 1958, a 7 mm. end-to-side shunt was constructed. Portal pressures were not recorded because of mechanical difficulties but the splanchnic veins were noted to be considerably less engorged after the shunt. The liver was cirrhotic and its caudate lobe hypertrophied. Many dilated lymphatics up to 2 mm. size could be seen over the diaphragmatic surface of the liver and many large, flat lymph nodes were encountered in the hepatoduodenal ligament. A liver biopsy confirmed the diagnosis of chronic veno-occlusive disease.

The child was discharged 25 days after operation, and convalescence was unremarkable. Follow-up has been continued at 3-month intervals. She has grown normally, remained asymptomatic, and looks and feels remarkably well. On her last visit in March, 1960 (1 year, 9 months after operation), neither liver nor spleen were palpable and there were no remarkable physical findings. Barium study at this time failed to disclose any esophageal varices.

Case 2. R. C., a 20-year-old Chinese female, was admitted Aug. 13, 1959, because of hematemesis. She had been born prematurely at sea and fed on brandy supplements for the first few months of life. She had grown up in Jamaica but had not lived with her parents and her guardians knew very little of her antecedent history. Except for recurrent epistaxes she had enjoyed good health up to 1 week before admission. She had recently been using a nasal spray on a doctor's prescription and had not taken any aspirin in the preceding month. She had noted foul black stools and weakness, and 2 days before entry had begun to have repeated hematemesis.

She was admitted in shock and was treated by transfusions and a Sengstaken-Blakemore esophageal balloon for 4 days. No jaundice was present and the liver and spleen were not palpable. A few spider angiomata were noted above the nipple line and a loud continuous venous hum, heard best over the xiphisternum, was noted. During convalescence the patient developed ascites and pedal edema which regressed slowly. Barium studies confirmed the presence of large esophageal varices and an incompetence of the sphincter at the cardia was also found.

After preparation, on Oct. 10, 1959, an end-to-side portacaval shunt 1 cm. in diameter was constructed. Portal pressures were not recorded but the engorged omental veins and enormously dilated veins in the falciform ligament were noted to diminish in size after the shunt and the xiphisternal venous hum disappeared. A small amount of ascites was still present and many

Table III. *Mortality rate statistics*

Cause of death	*Total (%)*	*Acute phase (%)*	*Chronic phase (%)*
Ruptured esophageal varices	17	5	12
Hepatic decompensation	12	10	2
Other causes	4*	1	3
Total %	33	16	17

*Cerebral abscess, subdural hematoma, and lobar pneumonia (during anesthesia induction for splenoportogram).

Table IV. *Incidence of documented esophageal varices in 23 patients*

No. of patients	*How documented*
17	At postmortem (as cause of death)
2	At postmortem (incidental finding)
3	By esophogram
1	By esophagoscopy (esophogram equivocal)

Table V. *Incidence of gastrointestinal bleeding*

	No. of patients	*Living*
Documented at postmortem examination		
Died of esophageal hemorrhage	17	No
Documented by radiologic study		
Esophageal varices by esophogram	3	Yes
Duodenal ulcer	1	Yes
No pathologic changes	2	Yes
No radiologic study		
Helminthiasis	2	Yes
Hemorrhoids	1	Yes
Lost to follow-up without study	3	?
Total	29*	

*Total number of patients under study was 99.

Table VI. *Liver function tests, Case 1*

	1953	*1954*	*Preoperative (1958)*	*Postoperative*		*March, 1960*
				Immediate	*6 wk.*	
Bilirubin 1 min.	0.3	—	1.2	1.3	0.1	0.2
Total	1.0	—	2.9	2.6	1.1	0.8
Thymol turbidity	1.2-2.2	2.4	3.7	1.7	2.2	2.0
Cephalin flocculation	1+-3+	2+	—	—	—	—
Serum albumin	3.5	3.1	1.6	1.5	2.7	3.1
Serum globulin	2.2	3.7	4.0	3.5	4.1	4.8
Serum cholinesterase	0.4-0.7	0.6	0.6	0.4	0.3	0.3
Prothrombin time	16	15	13	17	—	—
Alkaline phosphatase	—	—	40-19	10	66	60

Table VII. *Liver function tests, Case 2*

	Admission	*Before shunt*	*1959*			*March, 1960*
			3 days after shunt	*3 days after boremia*	*4 wk. after shunt*	
Bilirubin 1 min.	0.4	0.3	2.6	5.3	0.2	0.2
Total	1.6	0.9	3.8	8.0	0.6	2.6
Thymol turbidity	1.4	1.4	0.6	1.6	2.9	4.1
Serum albumin	3.2	2.8	3.1	2.4	3.8	2.8
Serum globulin	3.3	5.0	4.6	4.1	5.0	4.9
Serum cholinesterase	0.3	0.2	0.3	0.3	0.3	0.3
Serum alkaline phosphatase	9	11	5	12	11	4
Prothrombin time	—	13	14	—	—	—

dilated lymphatics were seen over the diaphragmatic surface of the liver which was hard and small and finely nodular. Clear fluid could actually be seen to drip from the surface of the liver. Liver biopsy disclosed marked fibrosis, nonportal in type, as in veno-occlusive disease and an occluded hepatic vein was identified.

Two days after operation and for the next 5 days the patient had recurrent hematemeses which were poorly controlled by esophageal tamponade with the balloon. She became jaundiced and developed sacral edema, but was afebrile and pain-free and the subxiphoid hum reappeared, although it was muted. On Oct. 17, 1959, transesophageal ligation of 3 large columns of varices was performed. The bleeding was found to be from a shallow 5 mm. ulceration almost at the cardia and not actually located on a varix. It was speculated that this erosion may have been produced by an indwelling nasogastric tube in this patient with poor cardiac sphincter action and that the ulcer lay anatomically between the sites of pressure exerted by the gastric and esophageal balloons. After this operation the subxiphoid hum again disappeared and has not been heard since.

The patient was discharged on Nov. 26, 1959, after a subsequently smooth course during which the jaundice and edema disappeared.

There has been follow-up at 2-month intervals in the clinic and she has been symptom-free and very cheerful. Barium study 6 months after operation failed to disclose any esophageal varices and she was quite well when last seen 7 months postoperatively.

Case 3. J. D., a 5½-year-old girl, was admitted Nov. 9, 1959, for esophagoscopy and portacaval shunt.

The first admission had been in November, 1955, for veno-occlusive disease at age 1 year, 8 months. Without prodromal symptoms she had developed, 6 weeks before entry, sudden ascites and pedal edema. She had been fed on bush teas. She had hepatosplenomegaly with ascites, was not jaundiced or febrile. The ascites cleared spontaneously. Needle biopsy of the liver disclosed typical veno-occlusive disease with early fibrosis and results of liver function tests were fairly normal (Table VIII).

The second admission was in August, 1956, for traumatic hemarthrosis. Transient jaundice and ascites were noted. Hepatosplenomegaly was still present. The patient was lost to follow-up after discharge until the third admission in November, 1959. At that time the patient was in the cirrhotic phase of veno-occlusive disease. Barium studies disclosed equivocal changes suggesting esophageal varices. Five members of this child's im-

mediate family had died from esophageal hemorrhage and she had had recent epistaxes. Slight jaundice and a small amount of ascites with hepatosplenomegaly were observed on readmission. Esophagoscopy documented the varices and on Dec. 5, 1959, end-to-side portacaval shunt 6 mm. in diameter was constructed. Portal pressures could not be taken but diminution in the size of the omental veins was noted after the shunt. The liver was grossly cirrhotic. Hypertrophy of the caudate lobe was noted, as was dilatation of the lymphatics and enlargement of lymph nodes in the hepatoduodenal ligament. Liver biopsy showed marked fibrosis and cirrhosis as in veno-occlusive disease.

The child was discharged 33 days after operation. Convalescence was marred by pneumonia in the lower lobe of the right lung which yielded to penicillin therapy. She has been followed in the clinic at 3-month intervals, has grown normally, is entirely symptom-free, and feels quite well. Liver and spleen are still barely palpable and a barium study 4 months postoperatively showed peristent though smaller esophageal varices.

Case 4. D. R., a 12-year-old boy, was admitted Jan. 7, 1960, for portacaval shunt. He was first seen in Pediatric Clinic in August, 1959, with a history of recurrent ascites, fever, and jaundice for 10 years and blood in the stool for 4 months. At the age of 2 years he had been hospitalized for 3 weeks at another institution because of anorexia, fever, jaundice, and ascites of sudden onset. He had been fed on bush teas since being weaned. He was rehospitalized there for a week 1 year later for the same symptoms.

On initial examination here there was no longer jaundice or ascites but hepatosplenomegaly was noted and a barium study confirmed the presence of esophageal varices. After preparation, on Jan. 23, 1960, an end-to-side portacaval shunt of 9 mm. diameter was constructed. Marked portal hypertension was noted and the veins in the falciform ligament were numerous and large. A drop in portal pressure from 240 to 120 mm. saline was obtained. Dilated hepatic lymphatics were again noted and the caudate lobe so large that a generous V excision had to be carried out to protect the shunt. Liver biopsy confirmed the diagnosis of cirrhosis of the liver.

During convalescence the boy had a low-grade fever of 100° F. for 10 days after operation which subsided spontaneously and was never adequately explained.

He was discharged 22 days after operation. Follow-up has continued at monthly intervals since then. He is now entirely symptom-free but the liver and spleen are still palpable. A postoperative barium study carried out 5 months postoperatively disclosed no esophageal varices.

DISCUSSION

In veno-occlusive disease of the liver we are confronted with a number of difficult

Table VIII. *Liver function tests, Case 3*

	1955	*1956*	*Preoperative (1959)*	*Postoperative*		*1960*
				Immediate	*6 wk.*	
Bilirubin 1 min.	0.8	0.8	2.9-0.8	3.0	1.0	—
Total	0.9	2.0	3.9-1.5	7.3	2.0	—
Thymol turbidity	2.0	3.6	4.3-2.5	1.6	3.0	—
Serum albumin	2.8	3.6	3.0-3.2	2.7	3.4	2.4
Serum globulin	3.6	4.2	4.8-4.3	3.5	5.0	5.1
Serum cholinesterase	0.3	0.3	— 0.2	0.2	0.3	—
Alkaline phosphatase	—	31	29-20	10	18	24

Table IX. *Liver function tests, Case 4*

	1959	*Preoperative (1960)*	*Postoperative*	*6 wk.*
Bilirubin 1 min.	0.03	0.2	0.4	0.8
Total	0.03	0.4	3.0	2.5
Thymol turbidity	3.3	1.9	2.5	3.2
Serum albumin	2.8	3.0	3.7	3.6
Serum globulin	5.2	4.7	4.3	3.9
Serum cholinesterase	0.4	0.3	0.4	0.3
Serum alkaline phosphatase	28	20	13	26
Prothrombin time	—	15	—	—

problems. Despite a fairly accurate knowledge of pathogenesis, there is as yet no specific therapy for the acute phase. While this phase appears by and large to be self-limited, there is considerable morbidity and an appreciable mortality rate (16 per cent). No reliable means of preventing eventual cirrhosis has yet been developed and it is uncertain how often the patients will again take Crotalaria against all advice.

The clinical features of chronic cirrhosis produced by veno-occlusive disease are strikingly different in many ways from those encountered in other forms of cirrhosis. The onset appears to be more rapid and the course to death acclerated. What part malnutrition or re-exposure to plant toxins may play is not yet elucidated. Concomitant disease, particularly sickle cell dyscrasia, does not appear to be contributory. It is striking that we have seen only 1 patient with spider angiomata (a 20-year-old Chinese female) and no palmar erythema in either adults or children with veno-occlusive disease, although in adults with Laennec's cirrhosis, the incidence of these phenomena is said to be comparable to that of esophageal varices.[42] Many of our patients have dilated abdominal veins, frequently with a venous hum best heard at the xiphisternum. Some of these patients have been found to have extensive collaterals (measuring up to 5 mm. in diameter) in the ligamentum teres hepatis but nevertheless have portal hypertension severe enough to produce esophageal varices. The subxiphoid hum disappears after portal decompression.

We have not encountered any proved instances of ammonia intoxication either before or after portacaval shunting and have seen only 2 primary malignancies of the liver in association with cirrhosis in children. We have not seen any thrombosis of the portal, mesenteric, or main hepatic veins as occurs occasionally in the Budd-Chiari syndrome.[29]

All patients with acute veno-occlusive disease have presented with ascites, as have a smaller number of those with disease in the chronic phase. In the acute phase of veno-occlusive disease this has often regressed as abruptly as it started, without benefit of a low salt–high protein diet, diuretics, or intravenous protein supplements. The level of the serum albumin bears little relationship to the phenomena of ascites in most cases. We have noted dilated lymphatic channels over the surface of the liver and along the hepatoduodenal ligament, some of them measuring over 3 mm. in diameter. We have also observed fluid, presumably hepatic lymph, to drip from the surface of the liver. We have not yet investigated the metabolism of aldosterone in these patients but suspect, a priori, that the urinary levels of this hormone are high.[38, 39]

The mechanism of ascites formation and turnover is still uncertain. It is known that the lymphatics draining the liver are increased, dilated, and thick-walled[1] and that there is increased hepatic lymph flow in cirrhotic patients with ascites.[13, 24] It is known that there is not only presinusoidal arteriovenous shunting[20, 33] but also diminution in the size of the hepatic venous bed[34, 59] amounting to an outflow block. One of the many unknown factors is whether increased filtration pressure within hepatic sinusoids and capillaries leads to increased capillary permeability and extravasation through the liver capsule or increase in lymph flow, since there is no apparent correlation between the level of portal pressure and ascites.[16] It has been suggested that the ascites in this condition is due chiefly to transudation of fluid from extracellular tissue spaces in an effort to dilute hepatic lymph and that changes in antidiuretic hormone and aldosterone are secondary factors reflecting volume changes.[59] It is also interesting to note parenthetically that although end-to-side portacaval shunts were performed in our patients for varical decompression, none of them reaccumulated ascites postoperatively.

Esophageal varices may appear quite early in the course of veno-occlusive disease, even in the acute phase, and cause death from exsanguination. We have noted unruptured esophageal varices in patients who

died from hepatic failure during the acute phase. We have also had 5 deaths from varical hemorrhage during the acute phase and in 3 of these the total illness had lasted for only 1 week in one instance, 2 weeks in another, and 7 months in another. This is not surprising as unruptured esophageal varices have been noted on esophagoscopy in patients with acute viral hepatitis.[11] The prospect of any major operation in the acute phase of veno-occlusive disease is appalling, and we do not yet have supportive adjuncts such as infant-sized Sengstaken-Blakemore esophageal balloons.

In only 1 instance was esophagitis noted at postmortem and an incompetence of the cardiac sphincter of the stomach was noted in another patient with large esophageal varices. This recalls the suggestion that the presence of turgid esophageal varices with the concomitant mucosal congestion may predispose to gastric reflux and peptic esophagitis.[14] Apart from the fact that in the act of crying these children might tend to increase intravarical pressure, we can add nothing to the study of the factors primarily responsible for the initiation of varical hemorrhage. We have not undertaken gastric acidity studies but have found only 1 patient with a peptic ulcer. We are, however, now alerted to the possibility of esophageal hemorrhage in the patient with veno-occlusive disease who has concomitant epistaxes or is found to have a marked elevation of the prothrombin time or alkaline phosphatase level.

We do not as yet know whether any of our patients have developed esophageal varices which subsequently disappeared. There have been no reports of a series of patients with esophageal varices secondary to cirrhosis of the liver who have lived for a period of years without bleeding.[58] The number of patients with histologically verified cirrhosis who develop esophageal varices is high. By esophagoscopy 70 per cent of cirrhotic patients have esophageal varices regardless of clinical severity of their disease.[10] By postmortem studies the incidence varies with the size of study from 57 to 90 per cent.[3, 57, 58] Our own study of this aspect of veno-occlusive disease is not yet complete.

The prognosis of the cirrhotic patient with esophageal varices is poor. In various centers, death from esophageal bleeding has been found to vary from 60 to 80 per cent in the first year after diagnosis is made, and the larger the series, the higher this percentage.[44, 45, 51, 52, 58] Of the survivors, 50 per cent can be expected to die from recurrent hemorrhage.[52] In our own small series, a mortality rate of 74 per cent due to bleeding esophageal varices was found.

Although there are dissenters,[39] most surgeons recommend venous shunting in the treatment of bleeding esophageal varices associated with cirrhosis. This conviction is based on the very sound experimental and clinical experience of the pioneers in this field, notably Whipple[60] and Blakemore,[5] who repopularized portacaval shunting, and this has withstood the test of time and a multitude of ingenious research studies.[32, 36, 46] The operative mortality rate has declined steadily and experienced surgeons now achieve rates of 10 to 15 per cent.[4, 16, 17, 25, 32] The incidence of postshunt bleeding is 6 to 19 per cent[4, 17] and not only do very few patients die from this, but it has been demonstrated that they require considerably less blood replacement than control (unshunted) patients.[17, 43] It has also been shown that patients protected by such shunts have a better prognosis than controls. In one very large series of cases, 75 per cent of patients with shunts were alive 1 year after operation, whereas only 30 per cent of the controls had survived. After 5 years 57 per cent of patients with shunts were alive as contrasted with 20 per cent of the controls.[17]

This experience has led some students of portal hypertension to advocate prophylactic shunts.[12, 16, 58] Welch[58] has stated, "All patients with extra-hepatic portal obstruction and varices ultimately bleed, and there is reason to believe that all patients with varices as a result of cirrhosis will bleed if they live long enough and do not succumb to their liver disease first." Our experience

with veno-occlusive disease inclines us to this view and to concur with Palmer[41] that "an improving clinical state offers no assurance that varices are becoming smaller."

Most children with esophageal varices have extrahepatic blockade and can often be maintained until the age of 10 years before venous shunting is performed. The problem of esophageal varices in children with intrahepatic blockade, however, is different. As there is little medical therapy for such cirrhotic children, some have urged that venous shunts be constructed regardless of age.[21, 22] The chief objection to the portacaval anastomosis in children on theoretical grounds is the apparently fixed size of the communication created and the fear that this may not grow pari passu with the child. A shunt of 7 to 10 mm. can, however, be created in patients under the age of 10 years. It has been shown that by using interrupted sutures in aortic anastomoses in young animals, the orifice so created can be observed to increase in size with the passage of time.[28, 50] There have not been any reports on the behavior of venous shunts in young patients as they aged and we are conducting experiments in young animals at the present time to investigate this hypothesis.

The splenorenal anastomosis is falling into disfavor because of poor long-term results and has been abandoned in some clinics.[15, 19, 23, 30, 41, 48, 56]

The side-to-side portacaval anastomosis has many disadvantages both practical and theoretical[2, 6, 25] and we have therefore performed only end-to-side portacaval shunts, so far with gratifying results.

In the absence of infant-sized esophageal balloons we have resorted to transthoracic ligation of bleeding varices in some children with veno-occlusive disease but our experience with this has not been encouraging. If the shunts that are being created should eventually fail to produce continued portal decompression, we may have to consider esophageal resection with jejunal or colonic transplant.[18, 31, 37] In 3 of our 4 cases varices have disappeared on esophagram postoperatively but none of the patients have undergone subsequent esophagoscopy.

We have noted temporary deterioration in results of liver function tests after shunting but they have returned to preoperative status within 4 to 6 weeks. We have not so far noted any striking improvement in the results of liver function tests after this period in spite of the fact that all of our patients are thriving clinically and feel and look considerably better than before operation. This observation has also been made in adult cirrhotic patients by others[2, 16, 17, 33, 43] who have also noted that this inertia in the results of liver function tests may last as long as 3 years postoperatively or fail to improve further. The necessity for a more accurate and sensitive index of liver function is obvious.

SUMMARY

Veno-occlusive disease of the liver is a recently established disease entity. Its etiology, pathology, symptomatology, and natural history are discussed on the basis of 99 cases of this disease so far authenticated at the University College Hospital of the West Indies.

In the surgical literature the disease is being added to the list of causes of intrahepatic portal hypertension, and the cases of 4 patients are presented in detail in whom portacaval anastomoses were performed for the decompression of esophageal varices.

The surgical implications of this disease have been stated and some of the difficulties encountered in the treatment of portal hypertension in infants and children outlined.

We wish to acknowledge our debt to Dr. Eric Back of the Pediatric Division of the University College Hospital of the West Indies, to whose service many of the patients were admitted.

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Nevus giganticus pigmentosus with malignant transformation

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The giant pigmented "bathing trunk" nevus is of more frequent occurrence than is indicated by a study of reported cases in medical literature. The supposed rarity of this bizarre and disfiguring lesion can be attributed to the fact that case reports are not published as a rule unless complications occur such as the supervention of melanoma. For example, in a casual and incomplete review of recent literature reports of only 57 giant nevi were found. Ten or 17.5 per cent of the patients had developed malignant melanomas, most of which had fatal metastatic dissemination. Only 2 of the 10 patients with malignant transformation of their giant nevi were adults, aged 27 and 37 years, respectively. The remaining 8 melanomas made their recognizable appearance in infants and children. The commonly held opinion that a patient with a giant pigmented nevus is safe once adulthood has been attained is obviously not valid. In our personal experience 4 of the 5 malignant variants of the giant nevus occurred in adults. The incidence of reported melanomatous degeneration of giant nevi of the bathing trunk type in infants and young children appears unduly high in comparison with the usual incidence of melanomas, which appear with more or less equal frequency in patients from age 20 to 70 years.

From a study of a large series of giant pigmented nevi seen more commonly in children, it may be asserted that 95 per cent of these lesions are covered with excessive hair in their entirety or in portions of the growth. Here again is a repetition of the erroneously held opinion that hairy nevi are not prone to undergo degeneration or transformation into malignant melanoma. The pigmentary changes may be distributed throughout the cutaneous surface over the major portion of the trunk both anteriorly and posteriorly but more commonly over the back, shoulders, and buttocks. The giant nevus may be associated with discrete nevi in unusual numbers over the face and extremities. Café-au-lait spots as well as multiple foci of deep pigmentation and pigmented tumescences may be scattered in the skin over the body. A variety of additional cutaneous tumors is found to be occasionally associated, including lipomas, fibromas of various types and sizes such as neurofibroma and fibroma molluscum, as well as soft pedunculated tumors simulating pachydermatoceles. Some patients present the functional, atrophic, and vasomotor syndromes of von Recklinghausen's neurofibromatosis. Other associated congenital abnormalities are sometimes found, such as muscular atrophy, elephantiasis of the extremities, anatomic asymmetry (especially of the thorax and trunk), hypertrophy of the cranial bones, prognathism, high palatal arch, scoliosis, spina bifida, and meningocele. Subcutaneous hemorrhages into and beneath this massive tumor have occurred spontaneously, just as in certain cases of von Recklinghausen's disease.

The commonly held belief that giant nevi of the bathing trunk distribution do not become malignant has probably arisen because of the fact that in the great majority of instances the tumor is comprised of nevus cells of the intradermal type. The surface of the

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Fig. 1. Giant bathing trunk nevus in an adult woman. Intensely black in childhood, this nevus gradually lost its color during maturation until now it has become an aquiescent intradermal nevus.

tumor may be verrucous with superadjacent hyperkeratotic skin free of junctional cells. Small foci of junctional nevi occurring in this enormous skin tumor may not be clinically perceptible unless the entire specimen is closely scrutinized. When the entire nevus is removed surgically, multiple microscopic sectioning of the tissues may be required to detect the associated junctional component of the nevus. When biopsy material is offered to the pathologist, multiple biopsies from suspicious lesions may be indicated in order to rule out the presence of a junctional element or to establish the diagnosis of compound nevus.

The nevi of infants and children have an associated junctional element in 90 to 98 per cent of cases, but as the nevus evolutes toward maturity with the advancing age of the child, the majority of the lesions show a disappearance of the junctional element and become intradermal nevi. Allen[1] has demonstrated that 12 per cent of the intradermal nevi in adults contain a junctional element.

Fig. 2. Segmental excision of nevus giganticus. The principal bathing trunk nevus and the associated isolated nevi were removed in serial stages by surgical excisions followed by skin grafting. The cosmetic result will improve with aging.

2*A*

It is these compound nevi in which the potential for malignant transformation into melanoma exists in adults with a giant pigmented nevus. The most salient features of the nevus which shows distinct change with the advance from childhood to adult life are the intraepidermal cells and cells of the dermoepidermal junction which tend to retrogress with advancing age. As the nevus grows older it consists primarily of nevus cells within the corium with little or no evidence of a junctional proliferation. We have seen numerous examples of giant pigmented nevi of the bathing trunk type which are darkly pigmented during infancy and childhood and present clinical evidence of transformation into a lesion in which the pigment has faded in adult life until it is barely perceptible (Fig. 1). The patients themselves volunteer the information that their gigantic nevi have progressively shown marked lightening in color with advancing years, although this is not to be relied upon for the security of the individual.

From the point of view of physical health, the most hazardous complication is the transformation of this nevus into malignant melanoma. Infection, ulceration, and granulomatous changes in the convoluted pachydermatoceles occasionally occur in this type of nevus, with unpleasant and odoriferous complications which are not hazardous to the health of the patient.

A very important handicap to the developing child is the psychosomatic problem associated with the presence of this serious cosmetic blemish. Once the children become self-conscious of their disfigurement they sometimes have serious social and psychic inhibitions which become aggravated when the disfiguration is discovered and ridiculed by schoolmates. This stigma alone offers sufficient indication for early surgical intervention in children before the impact upon the child's psyche makes the little patient a social recluse. This particular expression of the development of the nevus does not have a hereditary tendency as far as the specific type

2B

2C

Fig. 3. Congenital bathing trunk nevus in infant (Case 1). Multiple prepuberal melanomas were removed during childhood. Patient died from cerebellar metastases at 16 years of age.

is concerned, although the frequency of inheritance of moles is generally admitted.

The advantages of removing the huge bathing trunk nevus in childhood include (1) removal of the hazard of transformation into malignant melanoma, (2) removal of the trauma to the child's psyche by the handicap of this gross disfigurement, and (3) better healing in childhood and improved cosmetic restoration with the aging of the scar.

Technique of segmental excision of giant bathing trunk nevus. The surgeon may safely cut through the nevus and excise an incomplete segment of it without fear that the surgical trauma might stimulate a malignant transformation. Our experience in numerous cases has indicated the safety of performing multiple staged operations for the removal of this nevus covering such a wide expanse of body surface (Fig. 2). The first operation is usually started just before the child becomes of school age. It may require 3 to 10 surgical procedures with application of split-thickness skin grafts in order to complete the total removal of the neoplasm. In 2 or 3 earlier instances we have attempted the removal of the tumor by the repeated use of dermatome excision, taking out a relatively thick segment of skin at disparate times but have abandoned the procedure as dangerous because of possible incomplete removal. Such therapeutic disciplines as electrocautery, electrodesiccation, and radiation therapy are contraindicated.

Treatment of malignant melanoma superimposed upon giant pigmented nevus. The customary wide 3-dimensional dissection is performed. The removal is carried below the fascia down to the muscle bed and the adjacent tissues are excised wide of the melanomatous focus. If the location of the melanoma is sufficiently close to regional lymph nodes draining the skin of the site of origin, then the principle of excision and dissection in continuity (monobloc operation) with removal of the adjacent lymph nodes is performed. This operation is carried out even in the absence of suspiciously enlarged lymph nodes. In the few instances in our experience we have advised the adult patients to consent to segmental block excision of the remaining portions of the bathing trunk nevus, but have not found them to be cooperative in accepting this elective and prophylactic measure.

To illustrate the potential hazards of malignancy in the congenital nevus giganticus of bathing trunk type, we present the case

histories of 5 patients, 1 an infant and the others adults, in whom melanomatous changes developed.

CASE REPORTS

Case 1. P. N. was first seen as a 6-week-old baby girl on Aug. 7, 1935 (Fig. 3). Her general health had been good with the exception of a birth injury to her right leg from which she appeared to be recovering. She presented an extensive light brown bathing trunk nevus over her entire back extending from the shoulders to buttocks. Scattered over the diffuse brown nevus were 40 or more coal black discrete lesions. Nine of the more prominent intensely black tumors were excised, of which 3 were diagnosed as melanomas by Dr. James Ewing. Because of the total extent of the lesions and the baby's age, no further surgical procedures were attempted until the child became older. During the next 18 months, the remainder of the discrete black lesions were surgically excised during 3 hospital admissions. Some were junctional nevi. Others were of the type we would now classify as juvenile or prepuberal melanoma and would be expected to behave as benign tumors. Roentgenograms of the chest taken at repeated intervals during the patient's life were always negative for evidence of metastatic involvement.

When the infant was 1½ years old she complained of abdominal pain and a tumor was palpated deep in the left side of the abdomen, corresponding to the site of the left kidney. A diagnosis was made of a probable Wilms' tumor. It was considered to be unrelated to the melanotic tumors of the skin. After preliminary x-ray therapy, a nephrectomy was performed, the kidney measured 9 by 7 by 5 inches and was largely replaced by a nodular tumor. Pathologic diagnosis was embryonal adenocarcinoma, grade 3. Convalescence after the nephrectomy was uneventful. The child remained well for 10 years after the removal of this malignant tumor.

During the period of adolescent growth, the original birth injury to the right leg had resulted in a congenital club foot. The child also developed radiation scoliosis as a result of the deep x-ray therapy previously administered. At the age of 13 years the radiation scoliosis was repaired by spinal fusion. Menstruation had its onset at the age of 13 years.

In 1951, at the age of 16 years, the patient was readmitted to the hospital for further segmental excision of the bathing trunk nevus. The microscopic picture was that of intradermal nevus with associated compound nevi.

Three months later, on May 29, 1951, she was admitted to the hospital with a history of intermittent convulsive seizures associated with mental confusion which had existed over a period of 34 hours. After appropriate neurological survey, a cerebellar craniotomy was performed. Biopsy of

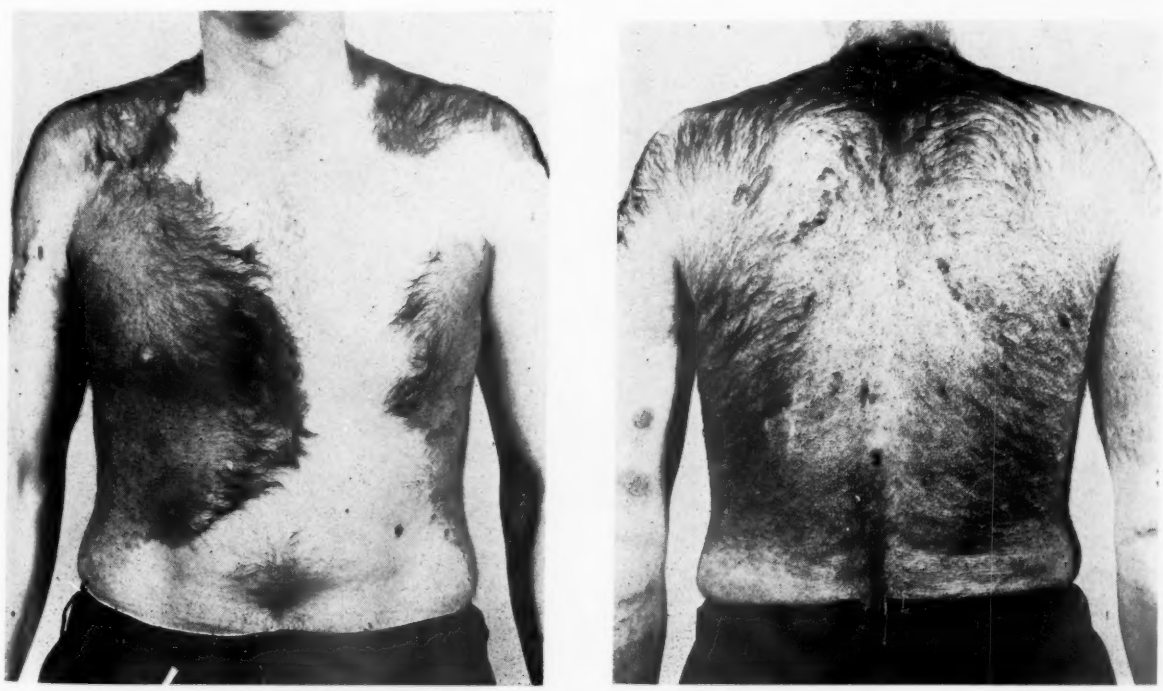

Fig. 4. Congenital bathing trunk nevus in young physician (Case 2). Infrascapular malignant melanoma associated with intradermal nevi containing foci of junctional change.

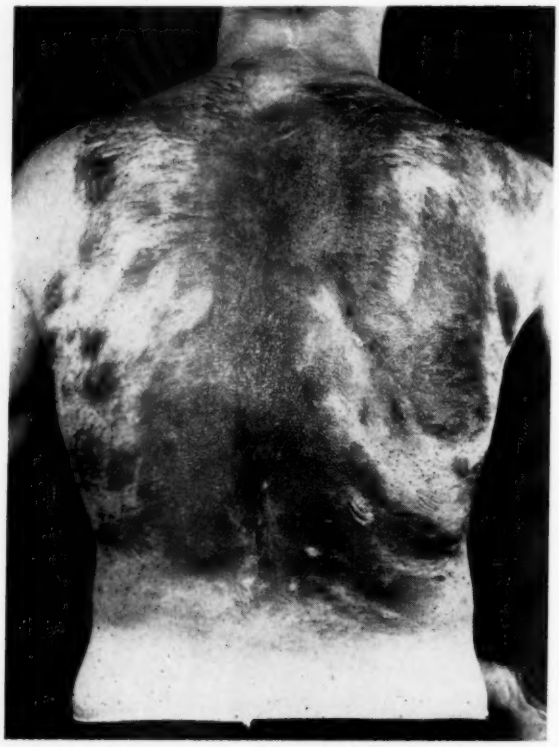

Fig. 5. Congenital bathing trunk nevus in young adult male (Case 3). Infrascapular malignant melanoma without metastases.

the diffuse inoperable cerebellar tumor revealed metastatic melanoma. The condition was slowly progressive until death on Oct. 23, 1951.

Case 2. W. M., a 28-year-old white male physician, was first seen on March 4, 1958. Physical examination showed a congenital hairy nevus of the bathing trunk type covering the entire surface of the back and extending laterally and anteriorly to partially surround the trunk (Fig. 4). Five years earlier, the patient had observed 2 nodules superimposed in the infrascapular segments of this giant nevus. In recent weeks both nodules had been locally excised in the hospital where the patient was serving his internship. They were diagnosed as malignant melanoma.

Review of the microscopic slides by Dr. Fred W. Stewart resulted in the opinion that one lesion was a nevus giganticus of questionable malignancy, but the second tumor had the appearance of a malignant Jadassohn's blue nevus, possibly capable of metastasis.

A roentgenogram of the patient's chest was negative for evidence of metastases. On March 4, 1958 the patient was admitted to the Memorial Hospital, where a wide 3-dimensional excision of the skin of the back was performed. Lateral sliding skin flaps after the manner of Celsus were devised to cover the defect.

Residual melanoma was found beneath the scar

Fig. 6. Congenital bathing trunk nevus in young adult male (Case 4). There is a malignant melanoma developing in the skin of interscapular region, associated with coexistent neurofibromatosis.

of one of the previous local excisions. The remainder of the specimen showed intradermal nevi with foci of junctional change. A series of segmental excisions with skin grafting was suggested for the future care of this patient. There has been no recurrence to date.

Case 3. H. S., a 32-year-old white male, was first seen on July 31, 1956. On examination, the patient had a congenital hairy bathing trunk nevus distributed solidly over the skin of his back (Fig. 5). As an infant, he had received radium therapy to several portions of the nevus.

Two and one-half months before the patient's initial examination, he had detected a new mole on his back. This nevus, about 1.5 cm. in diameter, was protuberant and on one occasion it had bled slightly. For this reason, he had consulted his local physician, who excised it. The report on microscopic examination indicated malignant melanoma.

The primary melanoma originated in the skin of the right infrascapular region about midway between the midvertebral and posterior axillary lines. At the time of the examination an oblique scar showed the results of excision, without clinical evidence of local recurrence. There were no suspiciously enlarged axillary lymph nodes.

On Aug. 14, 1956, a radical excision and dissection in continuity that included the old scar, the intervening skin, subcutaneous fat, and fascia as well as a right axillary dissection by the monobloc procedure were performed. The report on microscopic examination indicated malignant melanoma arising in a compound nevus. There were no metastases to axillary lymph nodes. The patient has accepted our advice to permit the surgical removal of the entire gigantic nevus with covering of the defect by split-thickness skin grafts and in a recent operation 50 per cent of the nevus was segmentally excised.

Case 4. M. O., a 38-year-old white male native of Russia, was first examined on July 5, 1927. He had an extensive congenital bathing trunk nevus which had caused no difficulty until 2 years previous to his examination (Fig. 6). At that time, he had noted a small enlarging lump in the midline of the interscapular region. It was surgically excised in another hospital and reported as malignant melanoma.

The bathing trunk type nevus almost completely covered the skin of the entire back with bilateral and supraclavicular extensions. The diffuse pigmentation was accentuated by innumerable elevated superimposed nevi of variable dimensions. The nevus was hairy and in color varied from light brown to black. Interspersed throughout the nevus were numerous, firm, subcutaneous and pedunculated masses typical of neurofibromatosis.

Fig. 7. Congenital giant nevus of back and buttocks in an adolescent girl (Case 5), with cerebriform convolutions and pachydermia. Recent nonpigmented melanoma is developing on left hip. Therapy was refused. (Lent by Dr. Zoilo Marinello Vidaurreta.)

Large, firm lymph nodes were palpable in both axillae. Radiographic studies of the lung, skull, spine, and other bone structures were normal at the time of the original hospital admission.

In the period between 1925 and 1931, x-ray therapy was commonly employed at the Memorial Hospital in the treatment of most metastatic cancers. Accordingly, between July 8, and Nov. 29, 1927, 8 x-ray treatments were given to each axillary region at widely disparate times. The factors were 180 KV, 35 cm. target skin distance, ½ c.mm. plus 1 mm. aluminum filter, 300 r equivalent at each exposure. On March 16, 1930, surgical exploration of each axilla was carried out for purposes of biopsy and to insert gold radon seeds into the axillary lymph nodes. In addition to the metastatic melanoma, clusters of nevus cells (benign) were gathered in the fibrous septa of the nodes, suggesting a primary development in this location (as determined by Dr. F. W. Stewart).

Metastases occurred in the calvaria, brain, humerus, bony pelvis, and scapula, with death ensuing on July 6, 1930.

Case 5. A Cuban child was born with a gigantic nevus occupying the entire lower back and buttocks. It became convoluted in huge folds during the growth of the child. It was associated with innumerable coal black pigmented nevi, probably of the junctional type, situated on the face and trunk. At the age of 16 the girl developed a rapidly growing, fungating, nonpigmented tumor on the nevus over the left hip (Fig. 7). At this writing, no surgical therapy has been given. This patient is under the care of Dr. Zoilo Marinello Vidaurreta, through whose courtesy the photographs are presented.

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Interscapulothoracic amputation for sarcomas of the upper extremity

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Pack and associates[1, 2] have reviewed the historical development, indications for, and operative technique of interscapulothoracic amputation. A clear understanding of the natural history and behavior of the offending tumor is needed for the performance of such a radical operation. In the usual course of events there is an initial refusal on the part of the patient to undergo the suggested interscapulothoracic amputation. Perhaps too few such procedures are carried out primarily, not only because of the patient's refusal, but also because of the surgeon's unwillingness to perform a deforming operation. The psychological effect in our 2 patients was good. They adapted readily to the loss of the upper extremity.

We are reporting 2 cases of sarcoma of the upper extremity with a long postoperative follow-up.

CASE REPORTS

Case 1. A 63-year-old woman was admitted to the University of Kansas Medical Center on Feb. 9, 1953. Her symptoms had begun in 1945 with the development of a small subcutaneous nodule in the upper arm. No biopsy was taken but she was given radiation therapy. During the next 4 years the tumor mass regressed slightly in size but never completely disappeared. In 1951 the skin over the anterior axillary fold became ulcerated and the arm was painful.

Physical examination showed an 8 by 12 cm. tumor mass over the upper medial deltoid area. The axilla was extensively scarred and bound to the chest wall. The center of the tumor mass was ulcerated with a peripheral circumferential field of radiodermatitis. Roentgenogram of the chest with particular reference to the scapula and the humerus failed to show any abnormality. A biopsy showed fibrosarcoma.

On Feb. 12, 1953, an interscapulothoracic amputation with resection of the anterior portions of the first to fourth ribs was performed (Fig. 1). This resulted in a 12 by 14 cm. defect in the anterior chest wall. A single layer of Fiberglas was sutured to the edges of this defect. This prosthesis was covered with a fashioned skin flap developed from the lateral and inferior portions of the arm. A catheter was inserted to drain the pleural space. Thirty-six hours after operation the postoperative course was complicated by fever and purulent drainage beneath the skin flaps and a culture showed the presence of a Proteus organism sensitive to Chloromycetin. On Feb. 29, 1953, the Fiberglas prosthesis was removed and the lung decorticated (Fig. 2). After this procedure recovery was uneventful.

Comment. This tumor was apparently malignant from the onset many years before its radical removal. It is interesting to speculate on the role of irradiation in the growth of this tumor. The postoperative infection may well have resulted from decreased tissue vitality secondary to extensive radiation therapy. The Fiberglas in the presence of an infection acted as a foreign body and had to be removed. The removal of the prosthesis destroyed a pleasing configuration of the shoulder. At the time of this report the patient has been free of disease for more than 7 years since resection.

Case 2. A 33-year-old white male was admitted on Feb. 11, 1955. Two years prior to admission he had noticed an enlarging mass in the right axilla. Since birth cutaneous nodules and pigmentation of von Recklinghausen's disease had been present over the entire body surface.

Previous history showed excisions of nonmalignant fibromas of the right arm in 1953, right ankle in 1937, and left side of the abdomen in 1940. No stigmata of this disease is present in other members of the family. On physical examination an 8 by 11 cm. movable axillary tu-

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Fig. 1. Interscapulothoracic amputation with resection of the anterior portions of the first 4 ribs. Planned flap from back of arm to provide skin cover.

mor was found to extend under the clavicle (Fig. 3). Muscle atrophy was present in the right upper arm. Weakness was elicited in the biceps, brachioradialis, and triceps muscles. There was no sensory loss. Chest roentgenograms were negative. The scapula, chest wall, and humerus showed no tumor invasion. A roentgenogram taken after a barium swallow showed irregularity of the cervical esophagus on the right (Fig. 4).

At operation the pectoralis major and minor were reflected from the humeral head. The sternoclavicular joint was severed and the clavicle reflected medially. The tumor mass was present between the cord divisions of the brachial plexus. The median and ulnar nerves were dissected from the tumor mass. A cervical tumor measuring 11 by 4 cm. was removed after detachment of the sternal attachment of the cleidomastoid muscle. The strap muscles were transected low in the neck. The internal jugular vein was ligated and divided. The tumor mass seemed to arise from the cervical sympathetic chain. The sternoclavicular joint was resutured with No. 3-0 stainless steel. The strap muscles and the sternocleidomastoid muscles were reapproximated. Postoperatively there were no neurological defects other than those noted preoperatively. Pathologic diagnosis of the removed surgical specimens was neurosarcoma. The patient was discharged on Feb. 24, 1955.

Nine months later the patient developed a recurrent 8 cm. axillary tumor (Fig. 5). He was readmitted on Nov. 15, 1955. Because of the previous diagnosis of neurosarcoma, it was explained that anything short of an interscapulothoracic amputation would not remove the tumor. The patient refused. On Nov. 16, 1955, the recurrent tumor was excised. A subperiosteal resection of the clavicle was carried out. The pectoralis major and minor axillary contents along with the tumor were resected. The tumor mass again arose from the median nerve in the axilla. Pathologic diagnosis was neurosarcoma.

Three months had elapsed when the patient noted recurrence of the axillary tumor which ulcerated and drained bloody fluid. On Jan. 5, 1956, an interscapulothoracic amputation was performed. The brachial plexus was severed high at the vertebral foramina. The axillary artery and vein were ligated distal to the thyrocervical axis, with preservation of only the transverse scapular artery to insure viability of the posterior shoulder flap.

Pathologic diagnosis was recurrent neurosarcoma. No regional nodes were involved. No vein invasion was seen. A wide adequate excision of the axillary tumor was now accomplished.

Seven months after shoulder girdle amputation a chest roentgenogram showed a soft tissue density (1.5 cm.) in the right upper lobe (Fig. 6). No local recurrence was present in the right side of the neck or shoulder. On June 21, 1956, a right fifth rib resection thoracotomy was performed. Segmental resection of the lateral anterior segment of the right upper lobe was carried out. No hilar adenopathy or other pul-

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Fig. 2. Appearance of chest wall after removal of the Fiberglas prosthesis and decortication of the lung.

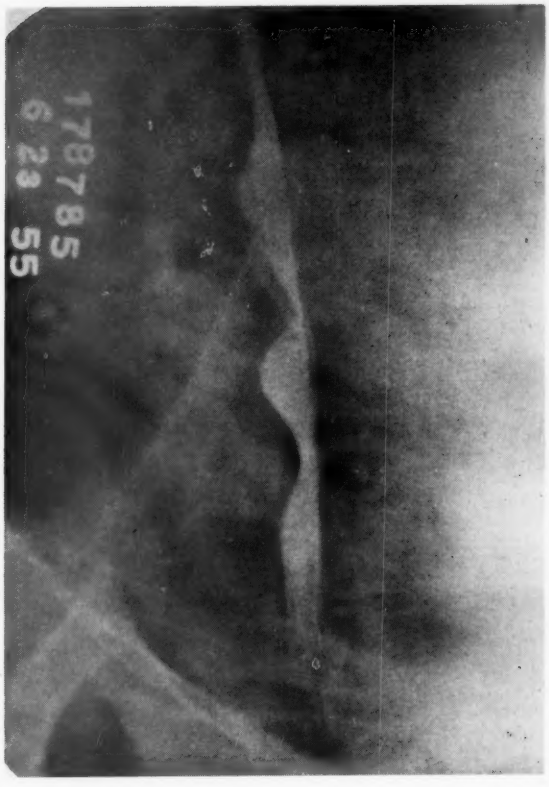

Fig. 4. Roentgenogram taken after barium swallow wich shows irregularity of cervical esophagus on the right.

Fig. 3. Preoperative appearance of axillary tumor.

Fig. 5. Recurrent axillary neurosarcoma.

monary metastasis was seen. The diagnosis was metastatic neurosarcoma. The patient was free of local and distant recurrence when last seen in June, 1960 (Fig. 7).

Comment. This patient with multiple fibromas carries a potential risk of recurring sarcomas. Persistence of surgical treatment to date seems justified since there is no recurrent tumor. Initial interscapularthoracic amputation would have been better treatment, but the patient refused. The

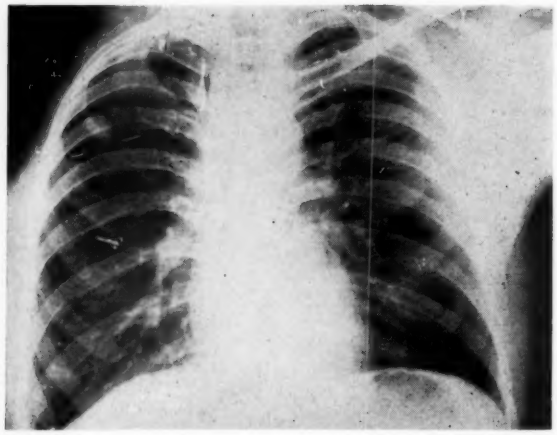

Fig. 6. Metastatic neurosarcoma in right upper lobe.

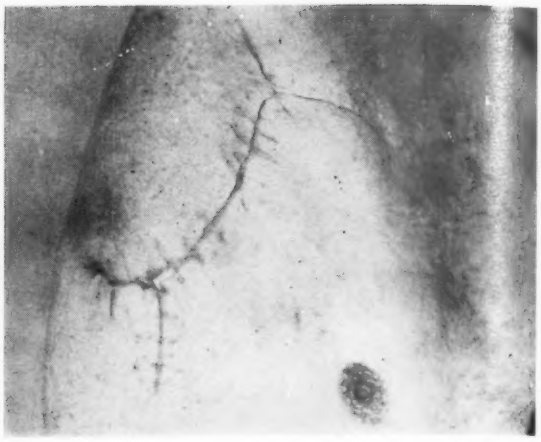

Fig. 7. Healed scar of interscapulothoracic amputation with no local recurrence.

original primary axillary tumor and the cervical and pulmonary metastases have been successfully controlled to date.

SUMMARY

Interscapulothoracic amputation for soft-tissue sarcomas of the upper arm and axilla, although deforming, results in palliation and cure. The persistence of treatment appears to be justified even though accessible, surgically removable metastases may develop.

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Bilateral radical neck dissection

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In the past 50 years the classical radical neck dissection has become a valuable part of the surgeon's armamentarium in his attack on carcinoma metastatic to the cervical lymph nodes. Crile[4] first advocated its use and it has been proved a worthwhile procedure by many surgeons. The removal of both the internal and external jugular veins is judged by most surgeons to be an important part of the operation because the deep lymph nodes adjacent to the internal jugular vein are commonly the seat of metastatic disease. The feasibility of sacrificing these principal channels of venous return on only one side has long been established. The ablation of these veins on both sides of the neck, however, has been considered an extremely hazardous and forbidding maneuver. For many years it was believed that an inevitable and irreversible elevation of intracranial pressure would result, with massive facial edema, violent nosebleeds, respiratory depression, and fatal intracranial hemorrhages.

Staged bilateral neck dissections were first performed in the 1930's. Martin[6] states that his first operation of this type was prompted by a young surgeon from Yugoslavia who had casually mentioned that his surgical chief in Belgrade had practiced such bilateral sacrifice with safety for many years. Subsequently, Martin removed the second internal jugular vein from a patient who some months before had undergone a contralateral neck dissection. Local anesthesia was employed and no untoward sequelae resulted. Since that time staged bilateral neck dissections with sacrifice of both internal jugular veins have been successfully performed by many surgeons. The fact that this can be done with a high degree of impunity and safety is not common knowledge among physicians. The optimum time interval between the stages has never been ascertained. Some surgeons prefer to wait 2 to 3 months and others believe that a period of 2 to 3 weeks is sufficient. The following discussion relevant to simultaneous bilateral neck dissection will indicate that the time interval between stages is of no great importance.

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CLINICAL EXPERIENCE

Our experience with this type of problem is based on 24 patients, 18 of whom had a two-stage bilateral neck dissection, and 6 of whom had a simultaneous bilateral neck dissection. Twenty-one of the patients were males and 3 were females. Their ages ranged from 31 to 77 years. Twenty-three had squamous-cell carcinoma and 1 patient had a malignant melanoma of the lip. Our first operation, a simultaneous bilateral dissection, was performed in January, 1950, by Dr. Rollin Daniel. It was performed 6 months after Perzik's[10] first operation, but without the knowledge that a simultaneous bilateral operation had ever been undertaken. There has been no hesitancy on our part in performing the two-stage operation. However, because of an unusual complication and fatal result in 1953, we hesitated for several years to perform further simultaneous dissections, especially if the larynx and strap muscles with their anterior jugular and other midline veins had to be sacrificed.

Fig. 1. Cerebral and cerebellar hemorrhages seen at autopsy.

CASE REPORT

A 61-year-old white male was first admitted to Thayer Veterans' Hospital on March 5, 1953, with a 6-month history of hoarseness and difficulty in swallowing. Three months before admission he had consulted a physician who had found a neoplasm in the hypopharynx and advised hospitalization, but the patient refused. Nodules had appeared in both sides of the neck and on admission one nodule on the right was the size of a golf ball. The patient was found to have a large squamous-cell carcinoma of the right pyriform sinus with bilateral cervical node enlargement. He was given 1,500 r tumor dose deep x-ray therapy to the hypopharynx, and on April 14, 1953, a bilateral neck dissection and total laryngectomy were performed. Postoperatively there was massive edema of the face, tongue, eyelids, and scalp. The cerebrospinal fluid pressure measured 600 mm. H_2O. By lumbar puncture this was reduced to below 300 mm. H_2O on numerous occasions during the next 3 days, but despite this the patient became comatose on the second postoperative day had convulsions, and died on the third postoperative day. An autopsy was obtained which showed severe cerebral edema, large subarachnoid hemorrhages, and hemorrhage within the brain (Fig. 1).

In this case one must conclude that the intracranial edema and hemorrhages resulted from the increased intracranial pressure subsequent to the ablation of the jugular venous system. Not until we were assured by Martin[7] that he and his associates had failed to experience similar lethal complications in an appreciable series of simultaneous bilateral neck dissections with total laryngectomies did we resume use of this operation. We believe, therefore, that such a complication with fatal outcome is the rare exception, and we have not hesitated in the past few years to perform this radical procedure.

The primary sites from which carcinoma metastasized to the neck in our 24 cases are listed in Table I. It is obvious that the site of origin would be in the neck or above, usually the oral cavity, pharynx, or larynx. Metastases from visceral carcinoma would not be amenable to neck dissection. In our experience, lesions of the larynx, hypopharynx, the floor of the mouth, and tongue have been those most frequently suited to bilateral neck dissection. Lesions at the midline or close to it frequently involve both sides of the neck with metastatic disease.

The operative procedure in the simultaneous dissections is of necessity prolonged and can be facilitated by the use of 2 teams. As the dissection approaches the midline, only 1 team can continue to work. We prefer an "H" type of incision, with the long transverse arm placed in the midneck and a diagonal incision extending from each end of it upward to the mastoid area and downward to the clavicle (Fig. 2). The lip may be split in the midline downward to the transverse incision when necessary and the tracheostomy may be placed through an oval window in the skin in the low midline (Fig. 3). Both sides of the neck are drained with

Table I. *Primary sites in patients with bilateral radical neck dissection*

Site	*No. of patients*
Larynx	12
Tongue	5
Floor of mouth	4
Lip	2
Nasopharynx	1

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Penrose drains and also with No. 18 Fr. catheters, which are attached to a negative pressure apparatus. Careful hemostasis is secured, the wounds are closed with silk in 2 layers, and firm pressure dressings are applied. These dressings are changed daily to insure maintenance of smooth, even pressure. The catheters have usually served their purpose by the second or third day, whereas the Penrose drains are left in place for from 4 to 6 days. Complete blood replacement and antibiotic coverage are utilized. We prefer penicillin and streptomycin, but when these cannot be used because of previous sensitization, we employ chloramphenicol or erythromycin.

The postoperative course, in spite of the lengthy operative procedure, is usually surprisingly smooth. Temperature elevation is rarely greater than 101 to 102° F. rectally, and the patient is out of bed and walking on the first postoperative day. Edema of the face, tongue, and lips is present to some degree in most cases after either the single or staged operation, but it is not troublesome and usually subsides in a few days (Fig. 4). We have the impression that the most extensive edema ensues in patients who have had deep irradiation therapy either before the second stage or before the simultaneous bilateral dissection.

Major wound infections have not occurred in any of the 24 cases. Other postoperative complications are summarized in Table II.

Of the 24 patients, 12 are dead at present and 12 are living, 10 of whom are free of disease. Follow-up of the 24 patients is shown in Tables III and IV. There were 2 operative deaths, 1 of which we would now avoid by routine tracheostomy. As far as we know, all deaths have been due either to carcinoma or to a complication after therapy.

DISCUSSION

In the past 15 years great strides in the radical surgical treatment of head and neck cancer have been made practical by better anesthetic techniques, adequate blood replacement, and the availability of antibiotics. It was inevitable that eventually simultane-

Table II. *Postoperative complications*

Site	*No. of patients*
Pharyngeal fistula	5
Pneumothorax	2
Cardiac arrest (1 survivor)	2
Postoperative hemorrhage	1
Cerebral edema and hemorrhage	1

Fig. 2. Extrinsic carcinoma of the larynx with bilateral cervical metastases.

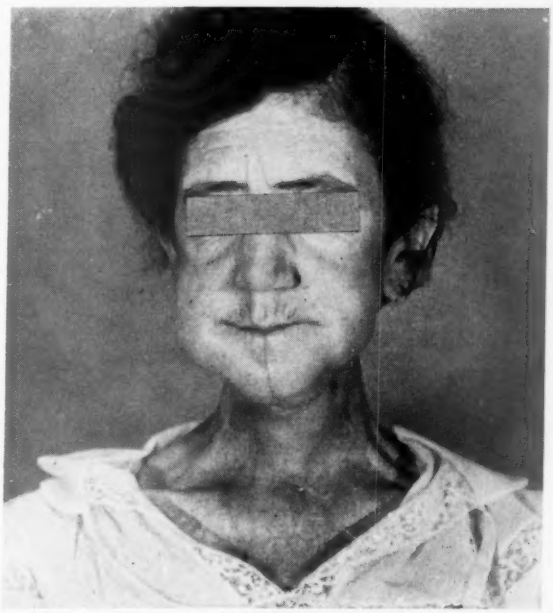

Fig. 3. Carcinoma of the floor of the mouth

Table III. *Follow-up of bilateral neck dissection*

Postoperative period	*0-6 mo.*	*6-12 mo.*	*1-2 yr.*	*2-3 yr.*	*3-4 yr.*	*4-5 yr.*	*Over 5 yr.*
Living (12 patients, 2 with disease)							
—	3	1	3	1	1	1	2
Dead (12 patients)							
2	0	5	3	1	0	1	—

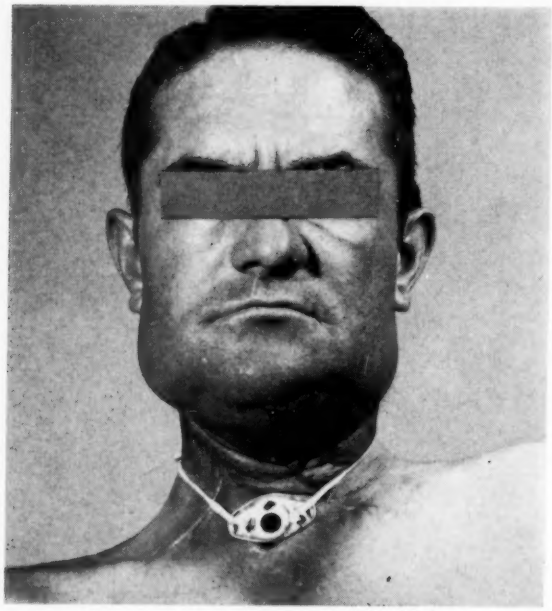

Fig. 4. Extrinsic carcinoma of the larynx with asymptomatic residual edema.

ous bilateral radical neck dissection should be performed. The first such procedure reported in the literature was performed successfully by Perzik[10] in 1949. In addition to the neck dissection, his procedure in this instance required a total laryngectomy with removal of the posterior third of the tongue. Thus, in addition to the removal of both external and internal jugular veins, the anterior jugular veins were also sacrificed. Though this procedure is not widely advocated, other surgeons[8, 9] have reported successful simultaneous bilateral neck dissections. Beahrs[3] reported from the Mayo Clinic 14 staged and 3 simultaneous bilateral neck dissections. Sugarbaker and Wiley[14] reported opposition to the procedure, and in 1956 Barbosa[1] stated his belief that the operation was dangerous and therefore he preserved one deep jugular vein. Royster[11] considered it desirable to insert a catheter into the spinal canal for decompression throughout the operation and for several hours thereafter.

Batson[2] estimated that the total cross-sectional area of the vertebral venous system alone is probably greater than that of the two internal jugular veins combined. Guis and Grier[5] experimentally demonstrated extensive collateral venous return from the head. Schweizer[13] studied spinal fluid pressures in a series of (1) control patients, (2) patients with unilateral neck dissections, and (3) patients with bilateral neck dissections performed in 2 stages or simultaneously. She reported no significant differences in spinal fluid pressures at the termination of the operation in any of these groups. Collateral venous return from the head after bilateral jugular ablation is primarily by way of the internal and external vertebral plexi, the occipital, posterior jugular, and the pharyngeal and esophageal plexi of veins. Schweizer,[12] in a review of 35 simultaneous bilateral radical neck dissections performed at Memorial Hospital in New York, reported 4 cases in which there was evidence of increased intracranial pressure. Only 1 death occurred and this was on the second postoperative day in a narcotic addict. To some degree, facial edema was present in practically all cases during the

Table IV. *Causes of death*

Cause of death	*No. of deaths*
Local bleeding and ulceration	5
Distant metastases	2
Respiratory	3
Cardiac arrest	1
Cerebral edema and hemorrhage	1

postoperative period, but it subsided and Schweizer believes the edema to be of little significance.

The second stage of a bilateral neck dissection should certainly be carried out when cancer-bearing nodes become evident on the contralateral side, presuming the nodes are deemed removable, and provided that the primary site and the side of the neck originally operated upon remain free of disease. Taken for granted is the absence of pulmonary or other distant metastases. Fixation to the carotid arteries is no longer a contraindication, for the external carotid can be safely sacrificed and a defect in the common or internal carotid arteries may be bridged with an arterial graft.

Bilateral simultaneous radical neck dissection is indicated in a patient with a potentially curable primary carcinoma and with palpable metastatic carcinoma to cervical nodes on each side. Prophylactic neck dissections, if indicated, should be staged. It is doubtful that so formidable a procedure is justified for palliation alone.

Certain precautions are indicated in the performance of both the staged and simultaneous bilateral dissections. A tracheostomy is mandatory. One of the early patients in this series, who underwent a staged procedure, died of a cardiac arrest after the contralateral neck dissection because a tracheostomy was not performed before the endotracheal tube was removed. The reverse Trendelenburg or upright position is of great help in aiding venous return from the head. The early recognition and prompt treatment of a pneumothorax, either unilateral or bilateral, may be lifesaving.[12] After ligation of the second internal jugular vein, bleeding is more profuse and, if feasible, this ligation should be postponed until late in the procedure. Other precautions are those normally observed in the usual unilateral neck dissection.

Even though nodes are enlarged and clinically contain carcinoma on each side of the neck there is often no extension below the clavicle. If the primary site is removable or has been successfully treated previously and a roentgenogram of the chest shows no evidence of metastases, the procedures outlined warrant strong consideration.

We grant that the procedures discussed are radical and the results certainly leave much to be desired. Treated less intensively, however, there is little doubt that all 24 of these people would be dead and would probably have died from local ulceration and bleeding. Such death is prolonged, painful, and horrible. Only 5 of our 12 deaths have been in such a manner. Thus, there is the possibility not only of cure, but also of increased longevity, and often of a less painful mode of death. We believe that these results justify either a single simultaneous or a multiple staged operation in properly selected cases. Patients in whom the disease is controlled are properly considered pure salvage.

SUMMARY

1. A brief review pertaining to the evolution of bilateral neck dissections, both staged and simultaneous, is presented.

2. Our experience with 24 such operations, 6 of which were performed in one stage and 18 in two stages, is discussed.

3. One case which had a fatal outcome due to an apparently unusual complication is outlined in some detail.

4. Bilateral neck dissection, in suitable cases, is strongly recommended.

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A method for chronic implantation of cerebral oxygen electrodes

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The problem of chronic electrode implantation has been approached in several ways, none of which have proved entirely satisfactory. The difficulties encountered are the shifting of the electrode, fragmentation of the leads, and insulation problems.

In order to implant glass-coated platinum electrodes into the substance of the brain and allow time for the effect of operative trauma to subside, a new method was devised. Glass-coated platinum electrodes were constructed with epoxy resin stabilizers. A stainless steel holder was devised to contain these electrodes.

MATERIALS AND METHODS

The operative implantation is simple (Fig. 1). A small trephine *(A)* with a guard *(a)* is used to make a hole in the skull at an appropriate spot. With a fitted key *(B)*, a threaded stainless steel cup *(6)* is screwed into the bone and remains in an extradural position. The electrode *(5)* is inserted through the cup and into the brain via a tiny incision in the dura. The external end of the glass is fitted with a rubber collet *(2)* that is slightly thicker than the cup. A threaded cap *(1)* is screwed down to compress the collet, thus holding the electrode tightly in place. The insulated lead *(3)* is bent over and the wound is closed. After healing has taken place, the lead may be connected to a suitable circuit for the recording of oxygen availability in the usual manner.

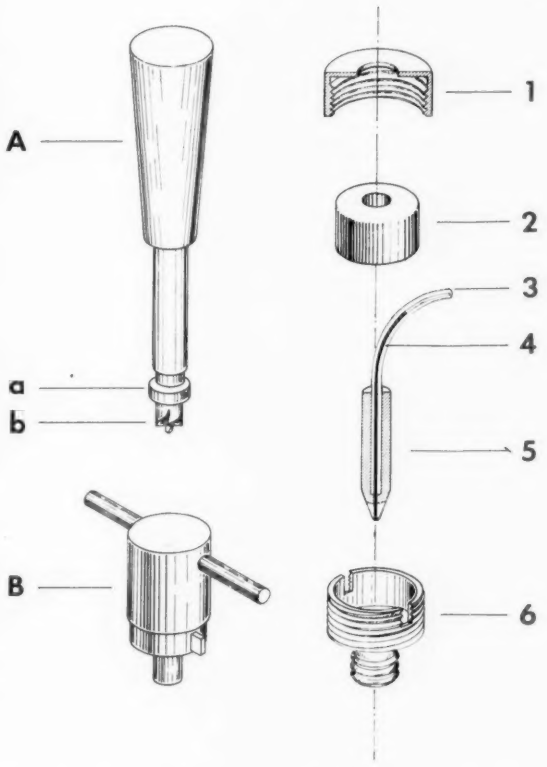

Fig. 1. Component parts of apparatus. *A*, Trephine; *a*, guard collet, *b*, cutting head. *B*, Key for insertion; *1*, threaded cap, *2*, rubber collet, *3*, insulation, *4*, platinum wire, *5*, glass-epoxy sheath, *6*, threaded stainless steel cup.

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RESULTS

The electrodes, as described were implanted in 4 dogs. A calomel reference electrode was placed subcutaneously at the time of measurement. Readings were taken with normal room air respiration as a base line. The animals were made hypoxic by apnea, excess oxygen was given by ventilation with 100 per cent oxygen, and a return to room air base line was permitted. Aside from the usual difficulties encountered with this type of electrode, placement presented no problems. After 7 to 10 days, no evidence of infection could be seen. The electrode and its holder were still solidly in place.

CONCLUSION

It is believed that this method of fixation may be extended for the placement of other electrodes or cannulae in any site overlaid with bone, such as sternal marrow cavity, long bone, or the cerebral ventricles.

Circulatory arrest during profound hypothermia induced by direct blood-stream cooling: an experimental study

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Since the pioneering investigations of Bigelow and associates[1] and Boerema and co-workers,[2] hypothermia and temporary circulatory arrest have proved valuable for open-heart surgery.[19, 28] However, it soon became apparent that ventricular fibrillation often occurred in man when temperatures of the body were less than 28° C., and without reduction of temperature below this level, prolonged circulatory arrest was not possible because of the risk of irreversible neurologic changes.

Direct cooling of the blood stream was reported as early as 1918 by Heymans,[13] who cooled and warmed the blood in a carotojugular shunt in more than 300 rabbits. Since then, many investigators have used arterial and venous cooling for experimental and clinical purposes.[2, 5] Venovenous cooling has been employed extensively by Brock and Ross.[3]

Gollan and associates,[11] in 1955, used a pump-oxygenator successfully to cool dogs to less than 10° C. and established prolonged circulatory arrest, with survival. Similar techniques have been studied by various investigators.[14-16, 25] Sealy and associates[24] have reported the combined use of extracorporeal circulation and hypothermia in man, but without circulatory arrest.

Shields and Lewis[26] and Drew and associates[8] simultaneously and independently described their technique for rapidly cooling dogs to 20° C. and establishing prolonged periods of circulatory arrest without the use of an oxygenator. Drew and Anderson[7] and Gordon[12] have adapted this procedure for open-heart surgery in man.

Since 1958 we have on occasion employed a pump-oxygenator for the purpose of inducing hypothermia and establishing circulatory arrest.[17] In order to obtain further information on extracorporeal cooling with the use of autogenous lungs, the present investigation was carried out in laboratory animals. The rate of survival was high.

EQUIPMENT

Two De Bakey roller pumps were used for the right-heart and left-heart circuits (Fig. 1). Mayon tubing with an internal diameter of 2½ inches was used for the right venous reservoir. The left venous reservoir consisted of Plexiglas tubing of similar size that incorporated an automatic level-sensing device for controlling the speed of the left-heart pump. A modified Brown-Emmons heat exchanger and a Gross filter and bubble trap were included in the left-heart circuit. Tygon tubing was used to complete the circuits.

The priming volume of the entire apparatus was 1,100 ml. The blood for this purpose was obtained from a mongrel dog which had been anesthetized with ether. Heparin, 3 mg. per kilogram of body weight, was injected intravenously before exsanguination.

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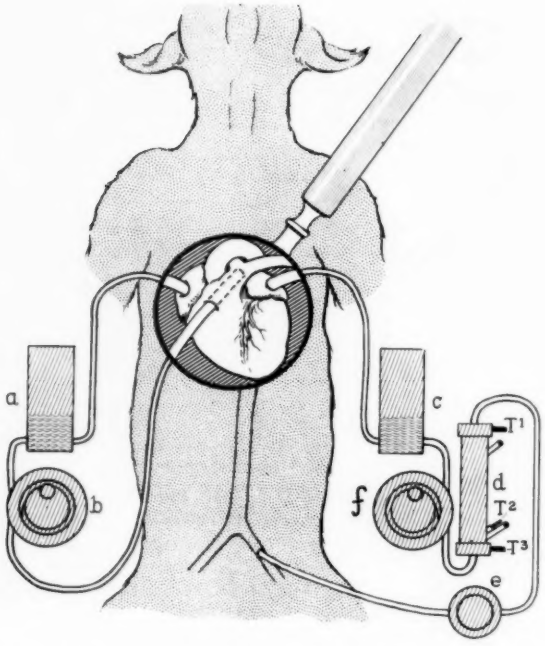

Fig. 1. Diagrammatic representation of circuits used for induction of profound hypothermia by direct blood-stream cooling. *a,* Right venous reservoir, *b,* right-heart pump, *c,* left venous reservoir, *d,* heat exchanger, *e,* filter and bubble trap, and *f,* left-heart pump. Thermistor positions for temperature recording were: T^1, blood leaving heat exchanger, T^2, water entering heat exchanger, and T^3, blood entering heat exchanger.

METHOD

In the first 36 animals used in the experiments (Group 1), repeated changes in technique were made as experience increased. After the method was standardized, 10 additional dogs were perfused (Group 2).

Mongrel dogs which weighed from 11.5 to 16.5 kilograms were intubated while awake, immediately after intravenous administration of succinylcholine chloride (2 mg. per kilogram). Anesthesia was then induced with nitrous oxide, oxygen, and halothane (Fluothane*) (1.0 to 1.5 per cent). A to-and-fro system with a soda-lime absorber was utilized. The dogs were hyperventilated by means of manually controlled respiration. Anesthesia was maintained with nitrous oxide, oxygen, and halothane (0.5 per cent).

*Fluothane used in these experiments was supplied by Ayerst Laboratories, New York, N. Y.

At an esophageal temperature of less than 28° C., hyperventilation was continued with 100 per cent oxygen.

Each animal was carefully secured in the supine position to prevent overstretching of the hind limbs. The chest and both groins were aseptically prepared. Both femoral arteries were exposed, and a plastic catheter was introduced into the right artery for measurement of the arterial blood pressure by a mercury manometer. Another plastic catheter was inserted into a jugular vein for the purpose of measuring the venous pressure with a water manometer.

Temperatures of the water and blood entering the heat exchanger, of the blood leaving the heat exchanger, and of the lower end of the esophagus were constantly monitored by means of thermistor probes.

The thorax was entered through a midsternal incision, and the pericardium was opened widely over the outflow tract of the right ventricle. The left femoral artery and both atria were cannulated 1½ minutes after heparin, 1.5 mg. per kilogram had been injected into the right atrium. The atrial cannulas were connected to their respective reservoirs, which were so placed that the level of blood was 32 cm. below the midlevel of the atria. This permitted adequate venous drainage by gravity. The apparatus was primed with blood, and the left-heart bypass circuit was completed. The right-heart circuit was completed later by cannulation of the pulmonary artery.

Left-heart bypass was then begun. Cooling was accomplished by reducing the temperature of the water in a stepwise fashion to 4° C. The right ventricle became inefficient at an esophageal temperature of 26° to 30° C. The pulmonary artery was then cannulated through a small incision in the right ventricle, and the right-heart bypass was begun. Cooling was continued until the temperature of the esophagus and of blood returning to the heat exchanger from the left atrium was approximately 15° C. Both pumps were stopped simultaneously, and circulation was arrested for 30 minutes. Ventilation was discontinued, and blood was allowed to siphon

from the animal into both venous reservoirs.

After 28 minutes, ventilation was restarted with 100 per cent oxygen. Two minutes later both pumps were turned on simultaneously, and the blood that had been drained into the reservoirs was reinfused slowly. Water at 15° C. was run through the heat exchanger for the first 2 minutes of reinfusion. The temperature of the water was then increased in a stepwise manner so that the gradient between it and the blood entering the heat exchanger did not exceed 12° C. The maximal permissible temperature of the water during rewarming was 43° C. (Fig. 2).

The heart was defibrillated at an esophageal temperature of 30° to 32° C. Shortly afterward the cannulas of the right side of the heart were removed, and the ventriculotomy closed. The left-heart bypass was discontinued when the esophageal temperature had remained at 37.5° C. for several minutes. Total loss of blood was assessed, and the volume of the blood was restored to the estimated normal value before the left femoral artery was decannulated. After removal of the cannulas, hexadimethrine bromide (Polybrene), 3 mg. per kilogram, was diluted in 100 ml. of 5 per cent dextrose solution and administered slowly intravenously.

A thoracic drainage tube was inserted through a separate stab wound. It was removed as soon as there was a threat that the animal would attempt to remove it. The dog was then returned to its cage. Blood was given to replace the postoperative loss.

Studies of acid-base balance were made on 3 animals. Samples of arterial blood were drawn just before cooling and immediately after completion of rewarming. Plasma pH was promptly determined on whole blood, at 23° C., by means of a Cambridge pH meter. The readings were corrected to 37° C. The

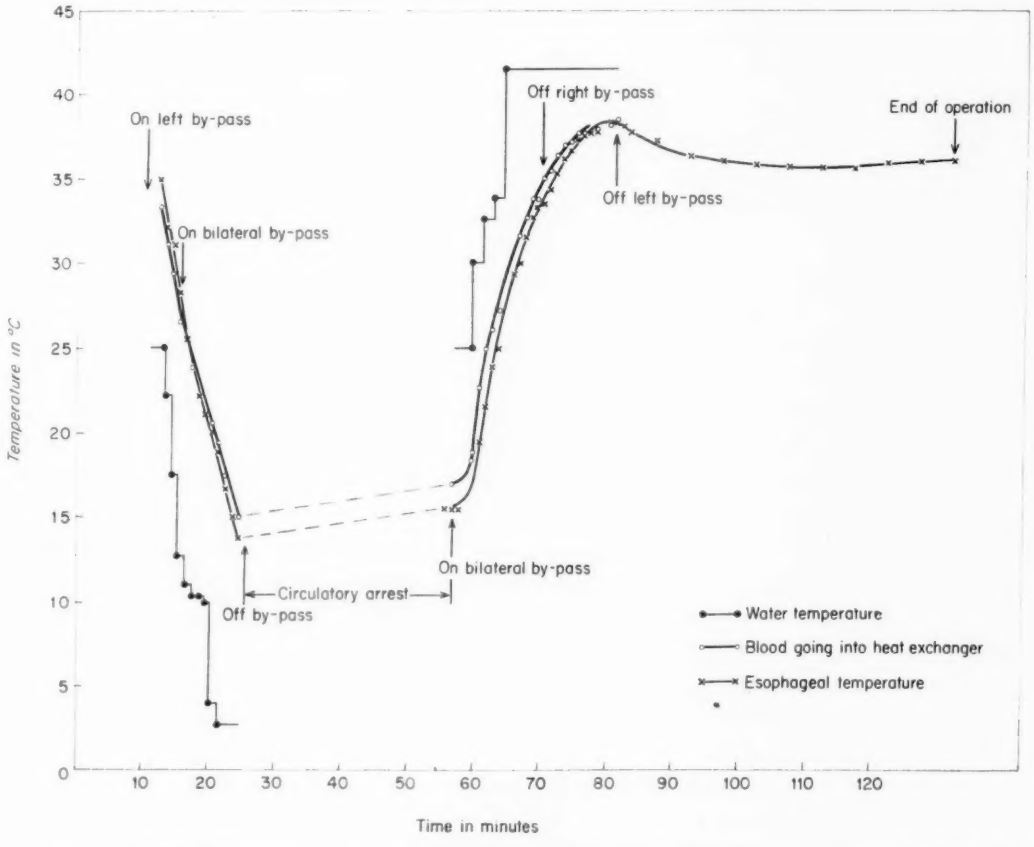

Fig. 2. Typical experiment in a dog cooled to 15° C. (blood entering heat exchanger), with 30 minutes of circulatory arrest. Note slight upward drift at the completion of cooling and slight downward drift at the conclusion of rewarming.

Table I. *Circulatory arrest during profound hypothermia; survival of dogs in Groups 1 and 2*

Experimental group	*Death due to avoidable technical error*	*Death within 72 hours*	*Long-term survivors*
Group 1			
Cooled to 20° C., with 20-minute circulatory arrest	2	1	4
Cooled to 15° C., with 30-minute circulatory arrest	4	12	13
Group 2			
Cooled to 15° C., with 30-minute circulatory arrest; procedure standardized	1	0	9

content of oxygen and carbon dioxide and the oxygen capacity of the blood were determined in duplicate with the manometric Van Slyke apparatus. The concentration of hemoglobin and the hematocrit value were calculated from the oxygen capacity of the blood. The buffer base and the carbon dioxide tension of the blood were derived from the nomogram of Singer and Hastings.[27]

RESULTS

Seven of the 36 dogs in Group 1 were cooled to 20° C., with circulatory arrest maintained for 20 minutes. Four of these dogs were long-term survivors, 2 died from avoidable technical errors, and 1 died from an undetermined cause (Table I). In the remaining 29 trials in Group 1, the animals were cooled to an esophageal temperature of 15° C. (range 13.8° to 15.8°), with circulatory arrest maintained for 30 minutes. Nine of these animals failed to survive the first 24 hours, 7 died between 24 and 72 hours postoperatively, and 13 were long-term survivors. The causes of death of the 16 dogs that died within 72 hours postoperatively were hemothorax and atelectasis in 7, technical errors in 4, damage to the central nervous system in 2, and undetermined causes in 3 animals.

All 10 dogs of Group 2 were cooled to 15° C., and circulation was arrested for 30 minutes. The arterial line was disrupted 3 times during rewarming in 1 dog, and this animal died 12 hours postoperatively, probably from air embolism. The other 9 dogs were long-term survivors. They were all active and looked normal when released from our care 3 weeks later.

The dogs of Group 2 weighed 11.5 to 16.5 kilograms, with an average weight of 13.53 kilograms, and the average surface area was 0.635 square meter.[18] The maximal flow rate for each dog varied from 120 to 184 ml. per kilogram per minute, with an average of 140 ml. per kilogram per minute, or 3 L. per minute per square meter. This maximal flow rate was usually reached after the pulmonary artery was cannulated. During perfusion the dog was transfused only sufficiently to maintain a satisfactory flow rate. A significant increase in flow rate was noted with transfusion of increments as small as 25 ml. As the cooling progressed there was a gradual reduction of venous return, without any external loss of blood, and consequently the flow rate fell. On rewarming, the reverse was true, as observed by Shields and Lewis.[26] The arterial and venous blood pressures during bypass in both cooling and rewarming phases were about the same as those before bypass, but there was probably some decrease in flow rate as cooling progressed.

The heart rate decreased during the period of cooling. When the right side of the heart was observed to be inefficient, at a temperature of 26° to 30° C., there was a drop in the venous return from the left atrium. Total cardiac bypass was then instituted. The heart was in complete arrest at an esophageal temperature of 14° to 19° C., although it still reacted to stimuli with a peristalsis-like movement. Spontaneous movement occurred at the rate of 1 to 4 times per minute during the first few minutes of circulatory arrest. No ventricular fibrillation was observed during the cooling phase.

During the rewarming phase the ventricles started to fibrillate vigorously at temperatures between 18° and 24° C. while the atria resumed independent, regular contraction.

Defibrillation was accomplished usually with 1 electric shock. In only 1 dog did fibrillation not occur during rewarming.

The temperature of the esophagus usually registered between 34° and 36° C. when cooling was begun. The time required to cool the animal to 15° C. ranged from 14 to 20 minutes, with an average of 17.1 minutes. Rewarming required a longer time in each case, the average rewarming time being 22.8 minutes (Fig. 2).

There was an average upward drift in temperature of 4° C. during the 30 minutes of circulatory arrest. After rewarming, there was a slight downward drift of an average of 2.7° C. from the time the animal was off the bypass to the termination of the operation about 40 to 45 minutes later.

Results of analysis of the blood indicated that there was respiratory alkalosis prior to cooling in all 3 animals tested (Table II). The buffer base in the 3 dogs was reduced before cooling, the average value being 38.9 mEq. per liter. Such values of buffer base have been noted after anesthesia and thoracotomy by others.[4, 22]

The buffer base was significantly reduced after rewarming in the 2 dogs tested. The pH was about normal because of the low partial pressure of carbon dioxide. No infusion of sodium bicarbonate was given to any dog.

All of the animals of Group 2 were awake at the end of the operation. Some degree of weakness of the hind limbs, lasting 1 to 2 days, was observed in 6 of the 9 long-term survivors. There were no signs of other neurologic deficits among the survivors.

COMMENT

Direct cooling of the blood stream is more efficient than surface cooling and affords more accurate control of the degree of hypothermia required. The differential temperatures of the various internal organs during cooling have been well recorded by various investigators.[16, 26] The rate of cooling of the various organs will depend on (1) total blood flow, (2) the distribution of the blood flow, (3) the temperature of the blood entering the organs, and (4) the environmental temperature of the organs involved. Thus, organs with an abundant vasculature furnish the greatest surface area for caloric exchange with the blood.

During cooling with the heat exchanger inserted in the left-heart circuit, the cold blood enters the animal at a certain temperature. By the time this blood reaches the various organs, it will not be at the same temperature as it was at the point of infusion. As blood travels through the aorta, thermal equilibration with the surrounding tissues occurs. Thus, blood entering the brain will be slightly warmer than blood entering the kidneys and liver.

It would be convenient if the temperature of one organ, for example the esophagus, would furnish a reliable indication of the temperature of the more inaccessible organs, particularly the brain. For this to be possible, both the distribution of the cooled perfused blood to the various branches of the aorta and the relative size and weight of the various organs would have to be constant, so as to permit a constant gradient of temperature. Clearly this situation cannot be obtained in the body; however, the so-called core temperature may be monitored and the results interpreted as a guide to local temperatures.

In several dogs in Group 1, the rate of cooling as recorded in the esophagus was

Table II. *Circulatory arrest during profound hypothermia: acid-base balance in 3 animals*

	pH			*Buffer base (mEq./L.)*			*pCO_2 (mm. Hg)*		
Animals	*1*	*2*	*3*	*1*	*2*	*3*	*1*	*2*	*3*
Before cooling	7.54	7.48	7.53	40.2	36.5	40.0	10.0	10.1	10.5
After rewarming	7.34	7.38	*	34.2	33.0	*	12.6	12.3	*
Change	−0.20	−0.10	—	−6.0	−3.5	—	+2.6	+2.2	—

*Unfortunately, these tests were not performed after rewarming in third dog.

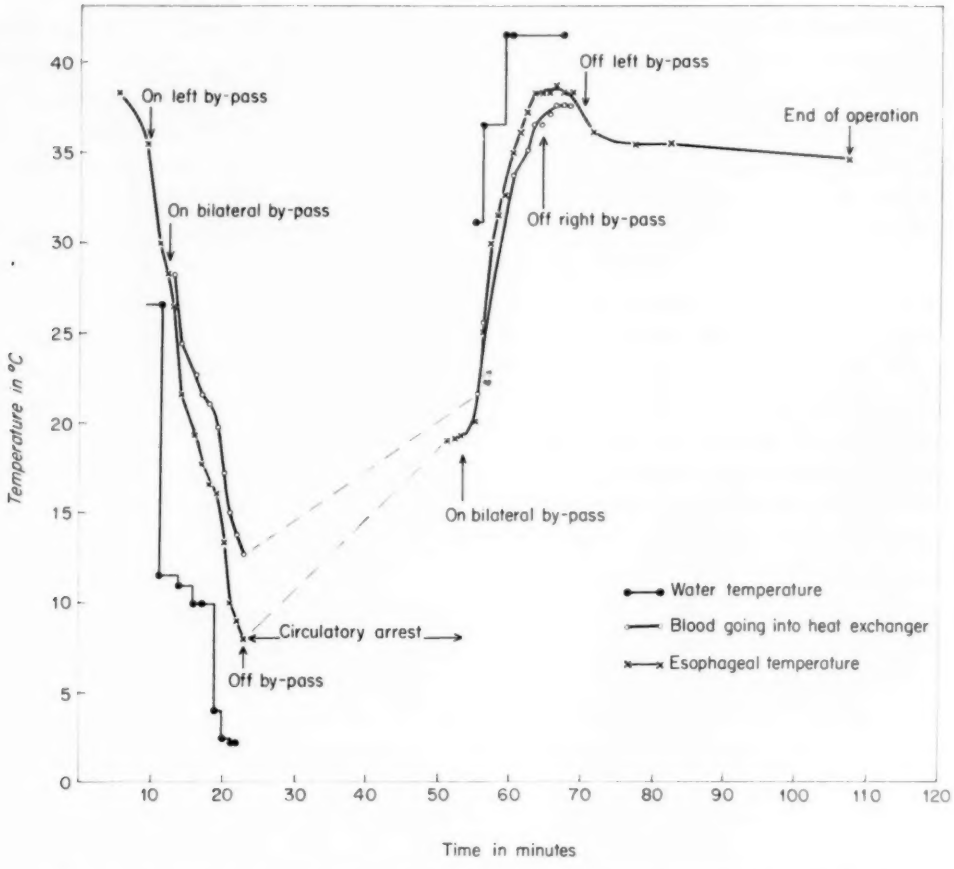

Fig. 3. A case in which cooling and rewarming were unusually rapid. There was considerable upward drift of temperature during the period of circulatory arrest.

unusually rapid (Fig. 3). None of the dogs were smaller than usual. Extracorporeal cooling was discontinued in 2 dogs when the esophageal temperature reached 15° C. within 5 minutes after cooling had been begun. After 30 minutes of circulatory arrest, the esophageal temperature showed an upward drift of 9.3° and 9.7° C. Both animals died from damage to the brain.

In Group 2 the temperature of blood drained from the left atrium was recorded, for purposes of monitoring cooling and rewarming, as it entered the heat exchanger. Cooling was discontinued when the temperature of blood entering the heat exchanger reached 15° C., regardless of the esophageal temperature (Fig. 2).

Donald and Fellows[6] showed that with changes in temperature, bubble formation may occur in a liquid when the tension of gas in solution exceeds the absolute hydrostatic pressure. Therefore, as a precaution against the development of gas emboli, rewarming was effected in stepwise fashion so that the temperature gradient between blood entering the heat exchanger from the lungs and water in the heat exchanger never exceeded 12° C. Rewarming in this way took only 3 minutes longer than was needed when blood was rapidly rewarmed with the water temperature constant at 43° C.; thus, little time was sacrificed by this extra precaution.

The presence of transient weakness of the hind limbs constituted the only postoperative complication observed among the dogs in Group 2. It has been noted that animals emerging from hibernation drag their hind legs for a few days.[10] Weakness of the hind limbs has been observed in rats after surface cooling,[21] and in dogs after profound hypothermia with direct cooling of the blood.[26] Clinically, it has been observed in patients

after surface cooling.[28] This could mean that hypothermia renders the peripheral nerves more susceptible to neuropraxia, or that there is a direct toxic effect of cooling on the peripheral nerves. Weakness of the hind limbs was less severe and of shorter duration when care had been taken not to stretch the hind limbs too tightly when securing the dog to the table. Previous experience showed that ligation of the femoral arteries in dogs does not result in weakness of the hind limbs.

The use of purely inhalational anesthesia seems to be advantageous in profound hypothermia. Agents such as nitrous oxide and halothane are quickly and entirely eliminated through the lungs. Elimination of intravenously administered agents, on the other hand, is partly dependent on detoxification in the liver, a function that is depressed by a reduction in body temperature.[23] The first few dogs in Group 1 were anesthetized with thiopental sodium or pentobarbital sodium and remained unconscious for several hours after the conclusion of the experiment. With the introduction of halothane, nitrous oxide, and oxygen, however, all dogs except those in which technical errors occurred during perfusion were awake and moving by the time the skin was closed. An anesthetic technique that enables the animal to regain consciousness immediately at the end of the operation is necessary for early assessment of the effect of hypothermia and circulatory arrest on the central nervous system.

Some investigators have used 5 per cent carbon dioxide in the inhalational gases in order to avoid respiratory alkalosis and to prevent an additional shift to the left in the hemoglobin dissociation curve,[20] especially since Fleming[9] and Swan and co-workers[28] found that animals appeared to tolerate low body temperatures better if the pH was maintained slightly above normal. All dogs in this series received 100 per cent oxygen during cooling when the temperature had reached 28° C. and again on rewarming until movement occurred. It was believed that the respiratory alkalosis produced would not itself be harmful and that it would compensate for the slight metabolic acidosis.

CONCLUSION

Although the risk of surface cooling is negligible when the cooling is done properly, the limited time for circulatory arrest permitted by this technique is not adequate for prolonged operations within the heart. The need for more time has to a great extent been satisfied by the use of a pump-oxygenator, and this procedure is associated with an equally low risk. Direct cooling of the blood stream with bilateral cardiac bypass and circulatory arrest must offer added advantages, without increased risk, if it is to be useful clinically. This method offers a number of advantages over the use of a pump-oxygenator in the usual manner. The equipment is simpler, the volume of blood needed for priming is smaller, and the operative field is truly quiet and bloodless. The disadvantages include the need for more numerous and difficult surgical cannulations. The present series of experiments has shown that the risk of the procedure in the normal dog is low.

SUMMARY

Circulatory arrest was established in 46 dogs after profound hypothermia had been produced by blood-stream cooling. In the first 36 dogs, designated Group 1, various changes in techniques were made. Seven of the animals in Group 1 were cooled to 20° C. and circulation was arrested for 20 minutes. Four were long-term survivors. The remaining 29 dogs in Group 1 were cooled to 15° C. and circulation was arrested for 30 minutes. Twenty of these animals survived more than 24 hours, and 13 were long-term survivors.

The procedure was standardized in the 10 dogs of Group 2—all animals were cooled to 15° C. and circulation was arrested for 30 minutes. Nine animals were long-term survivors, and the tenth died from an avoidable technical error.

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A study of left atrial pressures in profound hypothermia

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Distention of the ventricles, either during or immediately after total cardiac bypass, causes the chambers to resume their normal activity very poorly subsequent to bypass. This distention of the left side of the heart is reflected in the lungs by the development of pulmonary edema due to the backing up of blood into the left atrium.

Distention of the left side of the heart is particularly prone to occur in instances when the septa are intact, such as aortic stenosis and when cardioplegia is employed, even in the presence of septal defects. In the nonarrested heart with a septal defect, distention is usually obviated by the leaking of blood through the defect. However, it may be good practice to prevent distention in nonarrested hearts, when a tremendous bronchial return to the left atrium is expected (tetralogy of Fallot), by drainage of the left atrium.

Distention can be prevented with the use of a left atrial drainage catheter which is adjusted to drain when abnormal pressures within the chamber are present. We have used this precautionary measure often.

Recently, we have been using hypothermia as an adjunct in open-heart surgery in order to decrease the high flow rates usually necessary as has been proposed by Sealy and his group.[9]

In the laboratory while studying profound hypothermia with cardiopulmonary bypass, we noticed that many animals which were cooled to 7 to 10° C. with progressive arbitrary decrease in flow rates developed pulmonary edema shortly after the termination of the bypass. Since spontaneous cardiac standstill occurred between 18 and 23° C., the bronchial return to the left atrium could not be removed by the left ventricle. This occurred even when the aorta was not clamped. The left atrial pressure therefore may rise, causing pulmonary engorgement and pulmonary edema.

It is the purpose of this paper to present experiments performed for the study of left atrial pressures at various flow rates at normal temperatures and various hypothermic temperatures.

MATERIALS AND METHODS

Mongrel dogs which weighed from 14 to 20 kilograms were used. The animals were anesthetized with Pentothal sodium. An endotracheal tube was inserted and the animal placed on an automatic respirator which utilized compressed air. Bilateral thoracotomy in the fourth intercostal space was performed. A catheter was placed in the left atrium and was connected to a strain gauge. A single Bardic No. 20 to 22 catheter was placed in the right atrium. The pulmonary artery was cross-clamped and the venous return was collected by gravity into a reservior placed below the level of the table. The blood was returned through the left femoral artery and systemic blood pres-

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sure was recorded through the right femoral artery.

Two Sigmamotor pumps were used, one for pumping venous blood to the oxygenator and one for returning oxygenated blood to the animal. A 9-inch rotating disc oxygenator was used at 90 r.p.m. and 6 L. of 98 per cent oxygen, 2 per cent carbon dioxide was used as the oxygenating mixture. Oxygenated blood was passed through a single heat exchanger before entering the animal. Cooled or warmed alcohol-water mixture was circulated through the heat exchanger, which utilized a Thermorite unit.

Blood pressure and left atrial pressure were monitored before the perfusion and during the perfusion at different flow rates. The same studies were repeated during rewarming.

Six animals were studied. In addition, 1 animal was found to have heartworms in the right side of the heart and all branches of the pulmonary artery and was excluded from the series. In 3 animals the only variant was the temperature, with 3 different flow rates used at all temperatures. In 2 animals, atriotomies were performed and in addition to changing the temperature, we progressively decreased the flow rate (down to 10 ml. per kilogram per minute) in an attempt to keep left atrial pressure at low levels. One animal, No. 6, was perfused under the same conditions, but the left atrium was drained during the cooling and rewarming. The animals were then sacrificed and the lungs studied microscopically.

RESULTS

Studies of the left atrial pressure in the first 3 animals showed that as the animal became cooler and the heart became bradycardiac, the left atrial pressure rose. When the heart was arrested, the atrial pressure progressively rose as perfusion continued and was highest at the lowest temperature. After arrest occurred the heart was seen to distend slightly and as the perfusion was continued, this became more obvious. Upon rewarming, the left atrial pressure either remained elevated or rose until the heart began to beat or was defibrillated, at which time the pressure dropped and was low for the remainder of the perfusion. Table I shows the typical response in this group of animals.

In one of the dogs which had undergone atriotomy (Table II) an attempt was made to use left atrial pressure instead of blood pressure as an index of perfusion and to set the flow rate so that left atrial elevation would not occur. It was observed that even at a flow rate of 10 ml. per kilogram per minute the left atrial pressure was elevated. During rewarming, when fibrillation occurred, it rose to 20 to 25 mm. Hg, and when a regular beat was established by one defibrillatory shock, the pressure dropped to one-third the value.

In the other dog which had undergone atriotomy the left atrial pressure was

Table I. *Variation of left atrial pressure (L.A.P.) with temperature at different flow rates (Dog No. 3)*

	Flow rate						
	30 ml./Kg./min.		*40 ml./Kg./min.*		*60 ml./Kg./min.*		
Temperature (C.)	*B.P. (mm. Hg)*	*L.A.P. (mm. Hg)*	*B.P. (mm. Hg)*	*L.A.P. (mm. Hg)*	*B.P. (mm. Hg)*	*L.A.P. (mm. Hg)*	*Comments*
34°	70	4-6	—	—	—	—	Preperfusion
34°	80	4-6	85	5-7	90	5-7	
30°	65	6-9	75	8-10	75	5-8	
16°	40	9-12	40	10-13	40	12-14	At 25° C., fibrillation
10°	40	15-16	42	16-17	45	18	At 15° C., arrest
22°	70	7-10	90	6-7	95	7-9	At 22° C., beat
30°	65	10	65	11	65	11	
35°	90	7	95	7	102	7	
37°	90	8	—	—	—	—	Postperfusion

Table II. *Variation of left atrial pressure (L.A.P.) with temperature during atriotomy with progressive reduction in flow rate (Dog No. 4)*

Temperature (C.)	*Flow rate (ml./Kg./min.)*	*B.P. (mm. Hg)*	*L.A.P. (mm. Hg)*	*Comments*
35°	—	65	5-8	Preperfusion
28°	40	150	5	
22°	30	100	5-8	
18°	25	80	10-15	At 20° C., arrest
16°	20	60	10-12	
15°	15	60	10	
14°	10	60	12	
13°	10	25	12	
17°	20	60	12-15	
18°	20	60	20-25	At 18° C., fibrillation
23°	30	55	7-8	At 23° C., defibrillation
30°	50	130	—	

elevated to above 15 mm. Hg at 20° C. and the left atrium was decompressed by draining 60 ml. of blood from it. Arrest had occurred shortly before. The left atrial pressure fell to 8 mm. Hg and remained low. However, it was not drained further and pressure rose up to 12 mm. Hg at 10° C. At 23° C. when the heart was defibrillated upon rewarming, the pressure dropped from 10 to 5 mm. Hg as soon as an effective beat was established. At 30° C. with a normally contracting heart, even with high flow rates, the left atrial pressure was below 5 mm. Hg.

It appears from these experiments that a reduction in the flow rate alone cannot reduce left atrial pressure at temperatures below 20° C., but decompression of the left atrium with progressive decrease of flow rate will.

The changes in left atrial pressures seen after cardiac arrest and during rewarming upon beating or defibrillation are summarized in Table III.

Figs. 1 and 2 illustrate the lungs of 4 of the animals studied (Nos. 1, 3, 4, and 5) and of 1 control animal (No. 6) in which the left atrium was drained throughout the cooling and rewarming.

DISCUSSION

Langendorff[6] in 1895 observed the effect of hypothermia on isolated cat's heart, and observed, "that at even lower temperatures the heart muscle has not lost its excitability but that mechanical stimulations will be followed by very slow and weak, but still very distinct, contractions of the ventricle."

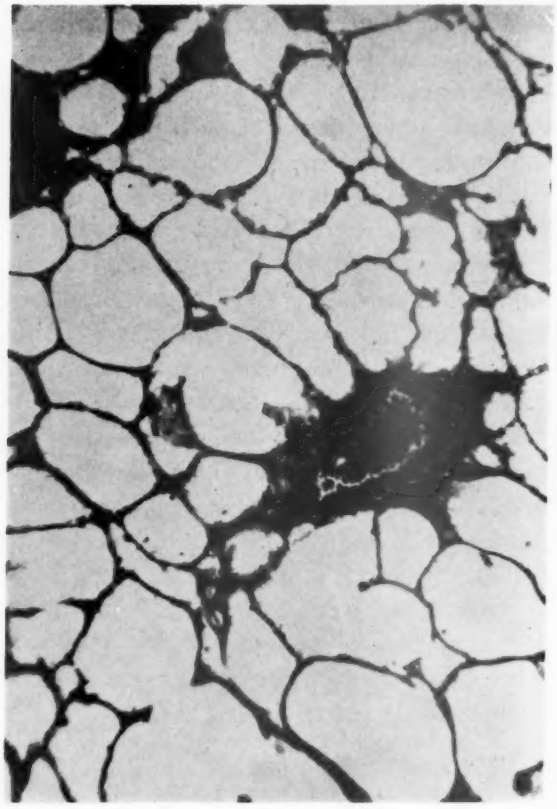
Under moderate hypothermia the heart maintains its efficiency for the demands at the low temperatures and myocardial function is not impaired. Solomon and Sayers[10] have observed that the work capacity of the intact rat's heart was more than 3 times greater at 32° C. than at 37° C. Reissman and Van Clitters[8] have noted that at any given work load, the efficiency of the heart at 28° C. was significantly greater than at 37° C. Berne[1] has shown that at temperatures down to 20.5° C., the myocardial function is not impaired. Covino and Beavers[2] noted a threefold increase in contractile force of the left ventricle with a reduction of temperature to 25° C. Goldberg[3] measured ventricular performance in hypothermia by measuring the contractile force of the ventricle by means of a strain gauge arch sutured to the ventricular wall.

Table III. *Changes in left atrial pressure (mm. Hg) with cardiac arrest and restoration of beat*

	Cooling		*Rewarming*	
Dog No.	*Before arrest*	*After arrest*	*Before beat (or defibrillation)*	*After beat (or defibrillation)*
1	4-6	6-7	9	6-7
2	4-5	9-11	13-15	10-12
3	9-12	15-16	15-16	7-12
4	6	12	22	7
5	—	15	8	5

A

B



C

Fig. 1. *A* and *B*, Sections of lungs of 2 dogs in which left atrial pressure was elevated during cooling and rewarming (no left atrial drainage). Lungs show extensive peribronchial and perivascular hemorrhage and hemorrhage into alveoli. *C*, Section of lung of dog in which left atrium was drained throughout cooling and rewarming. Alveoli are intact and there is no evidence of hemorrhage except for mild extravasation around the vessels.

The contractile force was increased in the right ventricle as the temperature was reduced and was maximum between 24° and 31° C. McMillan and associates,[7] measuring cardiac outputs on hypothermic animals, have demonstrated that there is no impairment of ventricular contractility at 28° C.

At temperatures below 20° C., however, as cardiac standstill is approached, the heart beats too infrequently and feebly to maintain an adequate output, even for the decreased demands at the low temperatures. Gollan[4, 5] observed that with total body perfusion and core cooling above 20° C., the heart contracts with sufficient frequency to eject the coronary and thebesian flow from the right side and the bronchial artery and thebesian flow from the left. Below 15° C., high flow rates and perfusion pressure should be avoided because they may cause dilatation and irreparable myocardial damage. Gollan

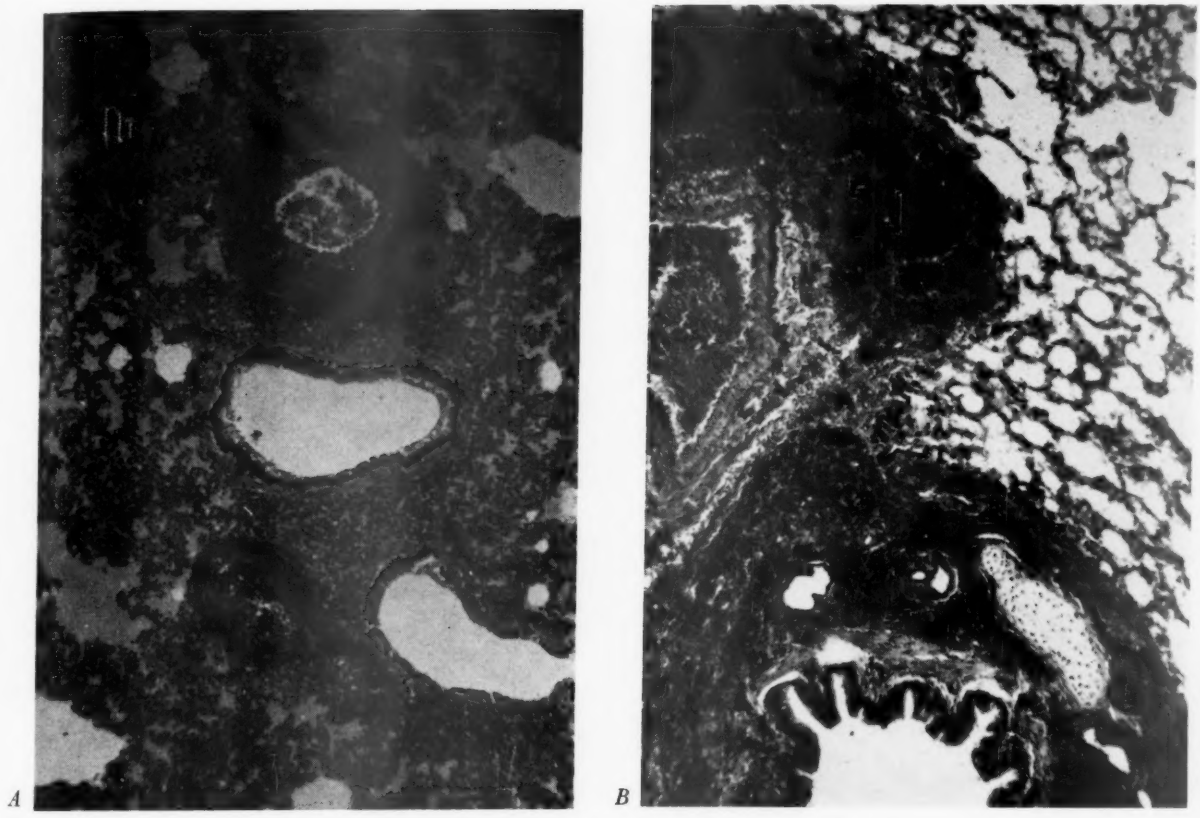


Fig. 2. Microscopic sections of lungs of 2 dogs in which left atrial pressure was elevated during cooling and rewarming (no left atrial drainage). The lungs show severe pulmonary congestion and perivascular and peribronchial hemorrhage.

suggests that at low temperatures there may be an increasing dilatation of the aortic ostium resulting in a functional aortic insufficiency.

When the heart goes into hypothermic arrest and the perfusion is continued, blood enters the left atrium through the bronchial return or, as Gollan suggests, through a functionally insufficient aortic valve. The blood cannot leave the left side of the heart which is not beating and in which the septa are intact, and it collects in the left atrium. As the perfusion is continued blood is continuously entering the left side of the heart and the left atrial pressure rises. Perfusion with high flow rates obviously increases any flow to the left side of the heart and progressive reduction in flow rate is essential when cooling to below 20° C. As the heart is cooled fibrillation will occasionally occur, which is followed by an elevation of left atrial pressure, as in arrest. When adequate heart action resumes upon rewarming and/or defibrillation, the left side of the heart ejects all the blood that has returned to it. The left atrial pressure drops and remains low for the rest of the perfusion.

Decompression of the left atrium during cooling and rewarming, however, will prevent distention of the left atrium with its resultant effects on the lungs.

SUMMARY

1. Changes in left atrial pressure were studied in 6 animals cooled to 10° C. or below with total body perfusion and a heat exchanger.

2. As cooling was carried to 20° C. a slight rise in left atrial pressure was seen. Below 20° C., as the heart approached hypothermic arrest and when arrest occurred, a significant rise in left atrial pressure was observed.

3. Decompression of the left atrium de-

creased the left atrial pressure and as long as decompression was carried out the pressure remained low.

4. All the animals which had elevation of left atrial pressures showed severe pulmonary congestion and pulmonary hemorrhage microscopically. In one animal which had decompression of the left atrium throughout the procedure, the lung appeared normal.

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Further studies of the effects of cardiac irradiation upon myocardial vascularity

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Previous reports[3, 4, 5, 6] have presented our results with the use of cardiac irradiation as a means of increasing myocardial vascularity in the normal canine heart. Survival studies, physiologic studies of intercoronary anastomotic blood flow, and pathologic examination in dogs after coronary occlusion have been consistent in their results. Animals which have received cardiac irradiation prior to acute ligation of the anterior descending coronary artery have demonstrated the protective effects of the radiation in all parameters. These animals have shown increased survival, increased intercoronary anastomotic blood flow and peripheral coronary pressure, and a greater vascularity as seen in plastic corrosion preparations and barium injection studies.

The present study was undertaken as a further severe test of the ability of cardiac irradiation to induce coronary arterial collateral circulation. Fineberg and co-workers[2] in a recent paper state, "Most of the experimental work done on revascularization of the myocardium of the dog is based on deliberate occlusion of the left anterior descending coronary artery, as a challenge to the procedure performed. . . . We believe that occlusion of the circumflex coronary artery just distal to its bifurcation from the left main coronary artery is a more critical test of the procedures being performed. . . . In over 100 surgical procedures no dog with complete arterial occlusion at this point has survived." If as previously demonstrated, cardiac irradiation produces intercoronary anastomotic blood flow which protects against acute occlusion of the anterior descending coronary artery, it should then theoretically protect against occlusion of the left circumflex artery. It was decided to subject the procedure of cardiac irradiation to the challenge of acute left circumflex coronary artery ligation.

METHODS

A total of 40 mongrel dogs were studied. Fifteen dogs received cardiac irradiation and were subjected to ligation of the left circumflex coronary artery at its origin 7 days after irradiation. Animals alive one-half hour after ligation were subjected to backflow and peripheral coronary pressure studies. The electrocardiogram was studied before and after ligation.

Each dog received a chest roentgenogram to determine heart location and size. The cardiac field was then mapped on the dog's thorax on both the right and left sides. The heart was irradiated by means of 6 alternating treatments to the chest fields during a 14- to 17-day period. The treatments were given with a parallel opposing pair of fields of 100 cm.^{2} The average separation of the fields was 10 cm. A cobalt 60 teletherapy unit was used to deliver a total estimated dose of 2,000 r to the myocardium.

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Table I. *A comparison of survivors after acute circumflex coronary artery ligation*

Group	*No. of dogs*	*No. alive 48 hours after ligation*	*% alive 48 hours after ligation*
Control group	25	2	8
Radiation group	15	6	40

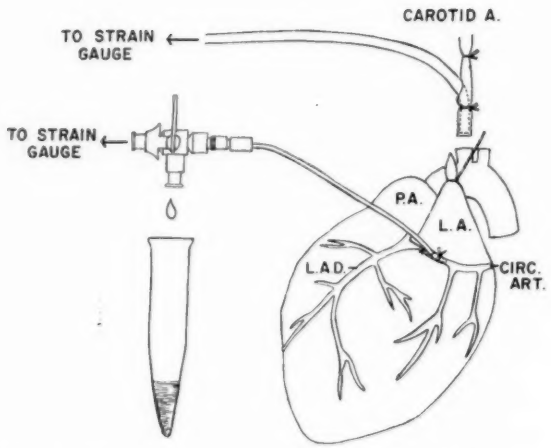


Fig. 1. Method of measuring peripheral coronary pressure and retrograde blood flow in the left circumflex coronary artery after coronary ligation. The blood flow through the coronary catheter during a 1-minute period is collected in a graduated cylinder. The mean aortic pressure is monitored by the carotid catheter.

Backflow and peripheral pressure studies were obtained by means of a catheter placed in the circumflex coronary artery just distal to the operative ligature. At a constant mean aortic pressure of 100 mm. Hg, as determined by a monitoring catheter in the carotid artery, measurements of the peripheral coronary artery pressure were observed and recorded. The retrograde collateral flow into the ligated left circumflex coronary artery was measured by collecting the blood flow through the catheter in a graduated cylinder for a 1-minute period at a mean aortic pressure of 100 mm. Hg (Fig. 1). Upon completion of these procedures the thoracic cavity was closed and the dogs were observed without further therapy. Upon death or sacrifice of the animal, a postmortem examination was performed, the hearts removed, and a vinyl plastic injection cast of the coronary circulation was made.

Twenty-five nonirradiated animals were subjected to the same studies and served as control animals.

RESULTS

The effects of acute ligation of the left circumflex artery as measured by survival of the animal 48 hours after ligation are presented in Table I. It is noted that a greater percentage of irradiated dogs sur-

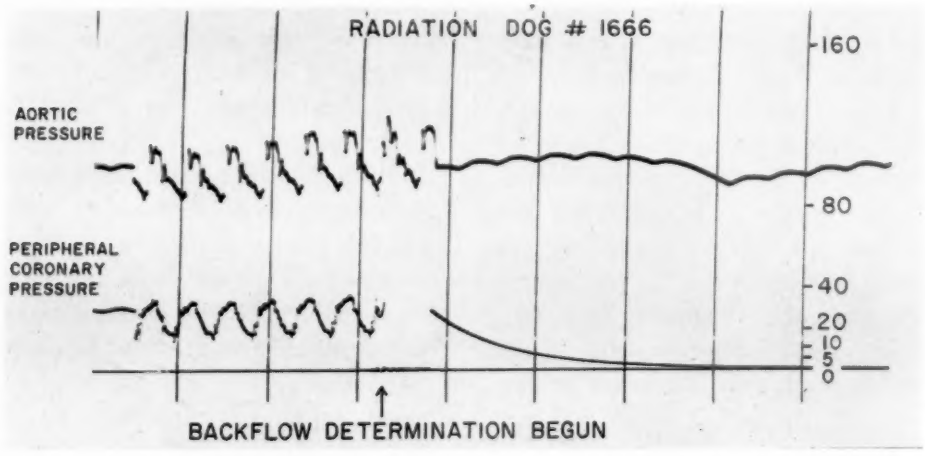


Fig. 2. Simultaneous recording of the aortic and peripheral coronary artery pressure distal to the ligature in the left circumflex artery 30 minutes after ligation. Note the mean aortic pressure is maintained at approximately 100 mm. Hg while the backflow determination is carried out.

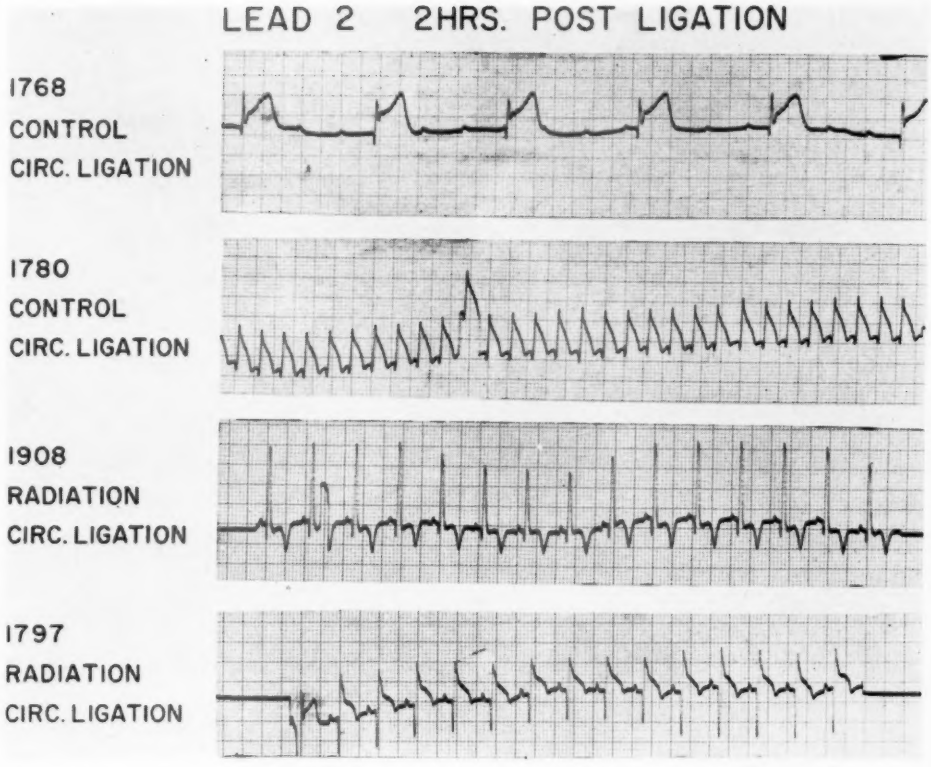


Fig. 3. Comparative electrocardiograms of control and irradiated dogs 2 hours after left circumflex coronary artery ligation. Control dogs exhibit high S-T elevations with complete heart block (No. 1768) and ventricular tachycardia (No. 1780). Tracings of the irradiated animals appear more normal after coronary ligation.

vived ligation than the nonirradiated control group. In 15 of 25 nonirradiated animals the heart did not fibrillate after acute circumflex ligation. However, only 2 (8 per cent) survived 48 hours or longer. In 6 of 16 irradiated animals studied, the heart did not fibrillate after ligation and all 6 (40 per cent) were alive over 48 hours.

To obtain a measurement of the amount of collateral intercoronary blood flow present at the time of ligation, retrograde blood flow and peripheral coronary pressure measurements (Fig. 2) were obtained one-half hour after ligation in all animals alive at this time. The data obtained are presented in Table II. A comparison of peripheral coronary pressure and backflow values in the ligated circumflex artery distal to the ligature revealed an average of 19 mm. Hg in nonirradiated animals at an aortic pressure of 100 mm. Hg contrasted to 22 mm. Hg in the irradiated animals. The average backflow value of all nonirradiated control animals studied was 2.2 ml. per 100 grams of heart weight. Irradiated animals exhibited an average value of 4.4 ml. per 100 grams of heart weight.

Electrocardiograms (Fig. 3) taken 2 to 7 hours after ligation in normal dog hearts which did not fibrillate showed the presence of severe infarctions with marked S-T segment elevations. In some tracings ventricular tachycardia, flutter with varying degrees of block, and complete heart block were noted. The electrocardiograms of irradiated animals also showed evidence of infarction but the S-T segments were not as sharply elevated and there were no arrhythmias present (Fig. 3).

Injection corrosion preparations of the ligated hearts revealed the irradiated hearts to have a more normal vascular pattern after coronary ligation than did nonirradiated hearts. The latter hearts (Fig. 4, *A*) exhibited large avascular cavities correspond-

Table II. *A comparison of retrograde coronary blood flow and peripheral coronary pressure after acute circumflex coronary artery ligation*

Dog No.	*Mean aortic pressure (mm. Hg)*	*Mean peripheral coronary pressure (mm. Hg)*	*Backflow (ml./min.)*	*Heart weight (grams)*	*Survival*
Control					
1780	100	18	3.0	157	4 hr.
1825	100	21	4.2	180	4 hr.
1823	100	25	5.4	193	8 hr.
1850	100	10	1.4	117	10 hr.
1988	100	20	4.0	145	15 hr.
1770	100	18	2.4	121	17 hr.
1824	100	20	2.3	108	25 hr.
1710	100	19	2.5	120	36 hr.
1777	100	20	2.5	162	2 mo.*
	Averages	19	3.1	138 (2.2 ml./100 grams heart weight)	
Irradiated					
1797	100	25	3.7	147	4 days
1666	100	30	9.6	131	4 days*
1644	100	19	2.4	123	8 days*
1882	100	18	4.6	85	3 wk.*
1908	100	20	3.6	81	3 wk.*
1798	100	20	5.0	91	2 mo.*
	Averages	22	4.8	109 (4.4 ml./100 grams heart weight)	

*Alive and well at this time. Sacrificed for pathologic study.

ing to the distribution of the ligated vessel. In the irradiated hearts (Fig. 4, *B*) the circumflex coronary artery and its branches distal to the point of acute ligation was filled by retrograde flow of the injected plastic from intercoronary anastomotic channels. These hearts were noted to be similar in vascularity to the normal nonligated heart (Fig. 4, *C*). An avascular crater was not seen.

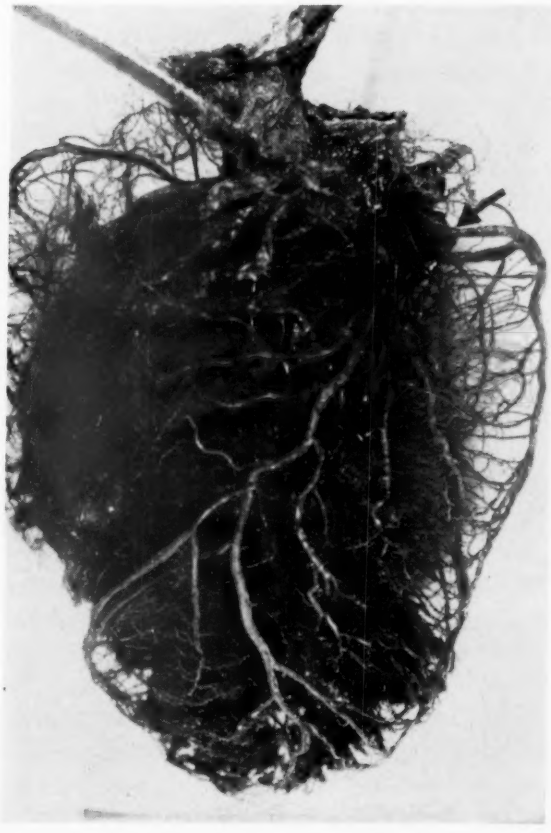
DISCUSSION

It is of interest that the values for survival and retrograde coronary flow obtained in the present studies after acute left circumflex artery ligation almost duplicate the figures derived from ligation of the anterior descending coronary artery.[6] Our survival rate in 50 irradiated animals after ligation of the anterior descending coronary artery was 40 per cent as contrasted to a control group survival rate of 11 per cent. In our present study after ligation of an entirely different major coronary vessel the survival among irradiated animals was also 40 per cent. Backflow values in the ligated anterior descending coronary artery averaged 4.1 ml. per 100 grams of heart weight contrasted with 1.2 ml. per 100 grams of heart weight in control animals. In our present study we obtained 4.4 ml. per 100 grams of heart weight as contrasted with 2.2 ml. in control dogs. This similarity in results would tend to bear out the premise that cardiac irradiation has induced a dilatation of the intercoronary anastomotic bed, thus accounting for increased survival rate and retrograde blood flow regardless of which portion of the heart vasculature is ligated. In the irradiated animals blood is able to flow into the ligated region in a retrograde fashion through functioning intercoronary anastomotic vessels as seen in the corrosion preparations.

Analysis of the backflow values and the corrosion preparations also explains the dif-

4A

4B



4C

Fig. 4*A*. Specimen of nonirradiated control heart after ligation of the left circumflex coronary artery. Note that a large segment of the coronary circulation is missing (outlined by dotted line). This corresponds to the distribution of the ligated vessel.

Fig. 4*B*. Specimen of irradiated heart after ligation of the left circumflex artery. The pattern of vascularity resembles that of a nonligated heart. The left circumflex coronary artery has filled in a retrograde fashion by means of functioning intercoronary channels. There is no avascular segment noted.

Fig. 4*C*. Vinylite injection and corrosion specimen of the coronary circulation in the normal dog's heart. Arrow indicates the left circumflex coronary artery.

ference in survival rates between irradiated and control animals. Although a high percentage of control hearts did not fibrillate after ligation of the circumflex artery and the dogs were in apparent good condition 4 to 36 hours after ligation, only 2 dogs survived over 48 hours. The retrograde blood flow into the infarcted area in these apparently healthy animals was only several milliliters per 100 grams of heart weight. The corrosion preparations bore out this paucity of vascularity and lack of intercoronary flow by demonstrating large avascular cavities corresponding to the distribution of the ligated vessel. These hearts, it would seem, did not have sufficient blood and blood distribution to continue to function. Some of the control animals, in apparently good condition, would die suddenly within the 48-hour period after ligation. In sharp contrast, all irradiated dogs in which the heart did not fibrillate in the first 30 minutes after ligation lived and were later sacrificed for other studies. Their backflow values and hearts gave evidence of greater intercoronary blood flow and better blood distribution. Electrocardiogram analysis also reflected the reason for the difference in survival. The electrocardiograms of irradiated animals did not exhibit the severe changes after ligation seen in equivalent control animals.

If in addition to our own control group we consider the survival and backflow data reported by other investigators after circumflex artery ligation, it would appear that irradiated animals exhibited increased survival and greater intercoronary blood flow. Our survival rate contrasts greatly with that reported by Fineberg and co-workers.[2] Beck[1] has reported an average backflow in dogs following his operation of 510 ml. per hour (8.5 ml. per minute). Irradiated dog No. 1666 (Table II) exhibited 9.6 ml. per minute per 131 grams of heart weight. The average backflow in normal dogs as reported by Beck was 228 ml. per hour (3.8 ml. per minute). However, no mention is made of the heart weight or the flow per 100 grams of heart weight.

SUMMARY

The effect of cardiac irradiation upon myocardial vascularity in the dog has been investigated by ligation of the left circumflex coronary artery and an analysis of survival, as well as subsequent electrocardiographic, physiologic, and pathologic changes performed. Irradiated dogs exhibited increased survival rates, better electrocardiograms, greater intercoronary flow, and more vascular hearts as determined by corrosion studies.

These experiments tend to independently corroborate similar findings derived from previous studies involving the anterior descending coronary artery.

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Technique of experimental ligation of the anterior descending coronary artery

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Ligation of a major coronary artery has been employed extensively as a method of evaluating the beneficial effects of the various techniques of revascularization of the heart.[3, 8-12, 18, 24] The mortality rate in dogs after acute occlusion of the anterior descending branch of the left coronary artery has been reported to range from 10 per cent to more than 90 per cent (Table I). The inconsistent results have caused this method to be subjected to much criticism.[7, 14]

If uniform results are to be obtained in repeated experiments, a landmark is necessary to guide the accurate occlusion of the coronary artery at the same level each time. The septal branch of the anterior descending coronary artery, which constantly arises near the bifurcation of the left coronary artery, lends itself particularly well as such a landmark.[5, 19, 23] The purpose of this presentation is to describe a technique of accurately duplicating ligation of the anterior descending branch of the left coronary artery. Variations in the anatomic relationship of the septal branch to the anterior descending branch are recorded.

METHOD

A dissection of the bifurcation of the left coronary artery, the circumflex branch, and the anterior descending branch with its septal tributary was performed in 45 dogs. In a series of 30 animals, the anterior descending branch was acutely ligated immediately distal to the septal branch without interruption of blood flow through the latter vessel.

Under sterile conditions with general anesthesia and controlled endotracheal respiration, the left side of the chest was opened and the pericardium incised. An incision was made in the epicardium superficial and parallel to the anterior descending coronary artery branch. By a combination of blunt and sharp dissection, the proximal portions of the two major tributaries of the left coronary artery were isolated and the septal branch identified (Figs. 1 and 2). The distance from the bifurcation of the left coronary to the septal branch was recorded and any anomalous tributaries of the anterior descending branch observed.

The anterior descending vessel was ligated with a No. 1-0 silk tie in approximation to the septal artery without infringement upon the patency of the latter branch (Fig. 2). Any anomalous branches of the anterior descending artery arising proximal to the septal branch were simultaneously occluded. Throughout the procedure and after closure of the chest, electrocardiograms were frequently obtained.

RESULTS

A septal branch, arising within 5 mm. of the bifurcation of the left coronary artery, was identified in each of the 45 animals. Approximately 50 per cent originated within the range of 2 to 3 mm. from the bifurcation with only 8.8 per cent arising at a point more than 3 mm. from it. Thirty-one per cent

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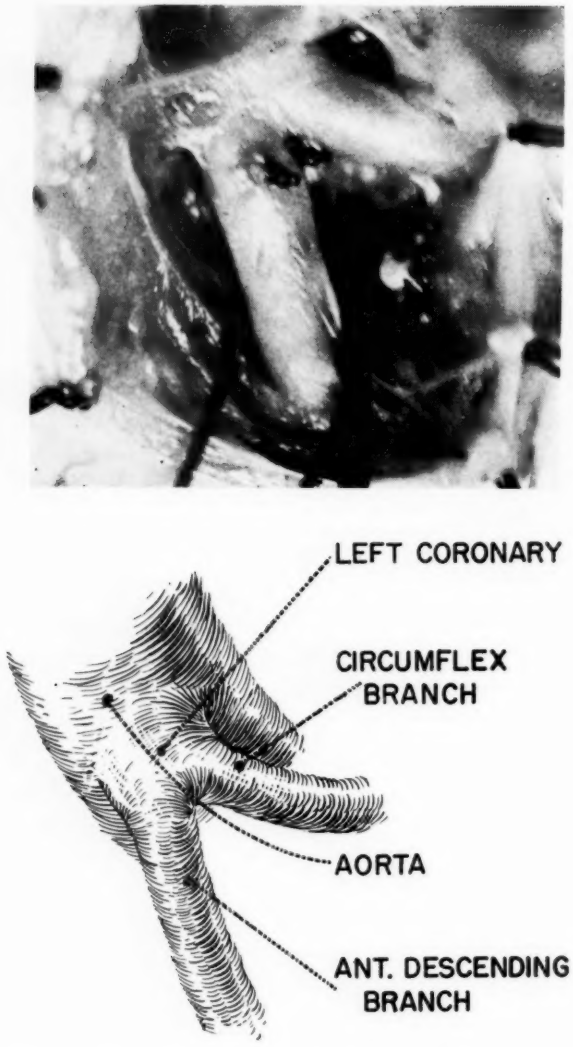

Fig. 1. The bifurcation of the left coronary artery and the proximal 2 cm. of the anterior descending branch have been exposed by dissection of the fat pad and epicardium from the superficial surface of these vessels.

Table I. *Mortality rates after ligation of the anterior descending branch of the left coronary artery in dogs*

Investigator	*Mortality rate (%)*
Manning[15]	10
Chardack[7]	10
Marcus[16]	23
Carter[6]	48
Bakst[2]	60
Minor[17]	63.5
Stanton[21]	70
Beck[4]	70
Vineberg[22]	90
Glover[10]	93

arose at the bifurcation of the left coronary artery (Table II).

Normally, no major tributaries arose from the anterior descending branch proximal to the septal artery. Anomalous tributaries of the anterior descending branch were observed in 8.8 per cent. The types of anomalies were accessory branches arising from the circumflex vessel or the bifurcation of the left coronary artery and an accessory septal branch (Table III and Figs. 2 and 3).

The mortality rate after acute occlusion of the anterior descending coronary artery in the series of 30 dogs was 76.7 per cent (23 deaths). Sixteen dogs died within 1 hour of coronary occlusion and 7 died between 24 and 72 hours after the operation.

Electrocardiography consistently showed evidence of severe myocardial ischemia within 5 minutes of coronary occlusion with marked abnormality of the S-T segment. With the exception of terminal ventricular fibrillation, arrhythmias were rare. Premature ventricular contractions which caused trigeminy were seen in several animals; however, in no instance did heart block result.

Seven survivors were eventually sacrificed and postmortem examination was performed in all cases. In every dog, the septal branch was demonstrated to be patent.

DISCUSSION

The type and depth of anesthesia, the technical dexterity of the surgeon, the speed of the operation, and differences in the distribution of the coronary blood supply are all factors which influence the inconsistency of results reported after this experimental procedure. However, the most important single factor determining mortality rate appears to be the level of coronary occlusion.[1, 23] The constant position of the septal branch of the anterior descending coronary artery, as further demonstrated by this study, makes it a readily accessible reference point for duplication of the level of coronary occlusion.

This site has been employed by other investigators[10, 13, 20] who stated that certain animals had to be excluded from their series

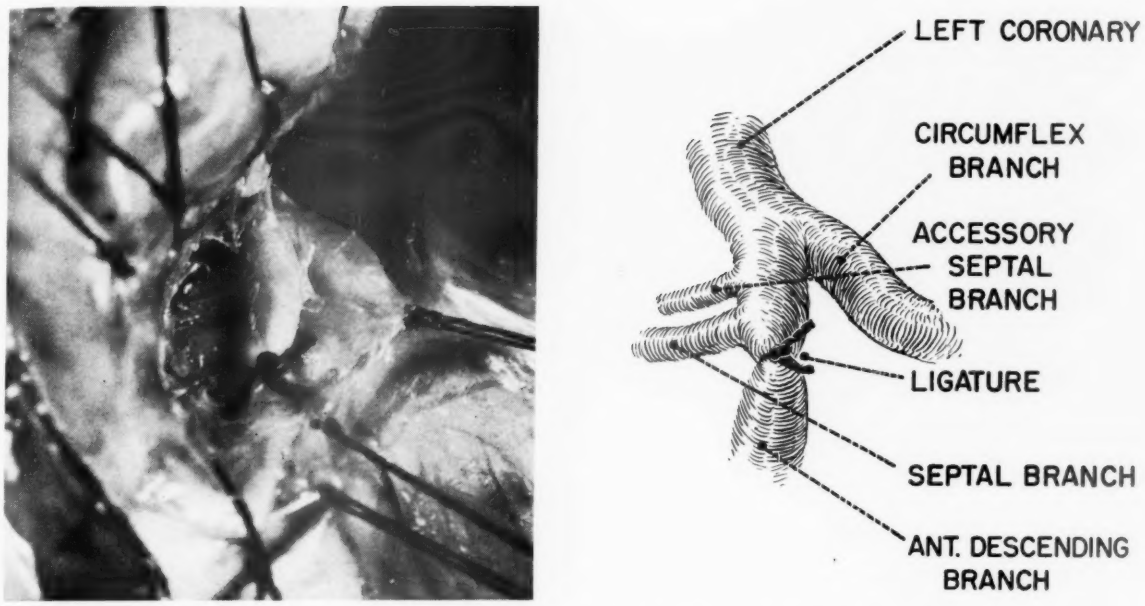

Fig. 2. A silk ligature has been employed to completely occlude the anterior descending branch of the left coronary artery without compromising blood flow through the septal branch. An accessory septal branch is present proximal to the main septal branch.

because the septal branch had inadvertently been ligated. To produce exact duplication of each operation, adequate exposure of all major tributaries of the left coronary artery is mandatory. The fact that in all instances in this series the septal artery was not occluded indicates the degree of accuracy obtained through sufficient exposure.

A mortality rate of 76.7 per cent after acute occlusion of the anterior descending branch compares favorably with rates reported by other observers which ranged between 70 and 93 per cent.[4, 10, 21, 22] Because of variations in technique, the exact mortality rate varies with different investigators; however, a method of controlling the major factor in mortality rate, the level of coronary occlusion, should increase the value of this experimental procedure.

CONCLUSIONS

The mortality rate after ligation of a major coronary vessel lends itself poorly to statistical analysis. However, the significant factor in the determination of mortality rate appears to be the level of coronary artery occlusion. Observations of the anatomy of the septal branch of the anterior descending

Table II. *Location of the septal branch of the anterior descending coronary artery (45 dogs)*

Distance from bifurcation of left coronary artery (mm.)	*No. of specimens*	*% of total*
— (arose at bifurcation)	14	31.1
1	5	11.1
2	11	24.5
3	11	24.5
4	2	4.4
5	2	4.4
Totals	45	100.0

Table III. *Anomalies of the anterior descending coronary branch (45 dogs)*

Type of anomaly	*No. of occurrences*	*Incidence of occurrence (%)*
Accessory branch from circumflex	2	4.4
Accessory branch arising at bifurcation	1	2.2
Accessory septal branch	1	2.2
Totals	4	8.8

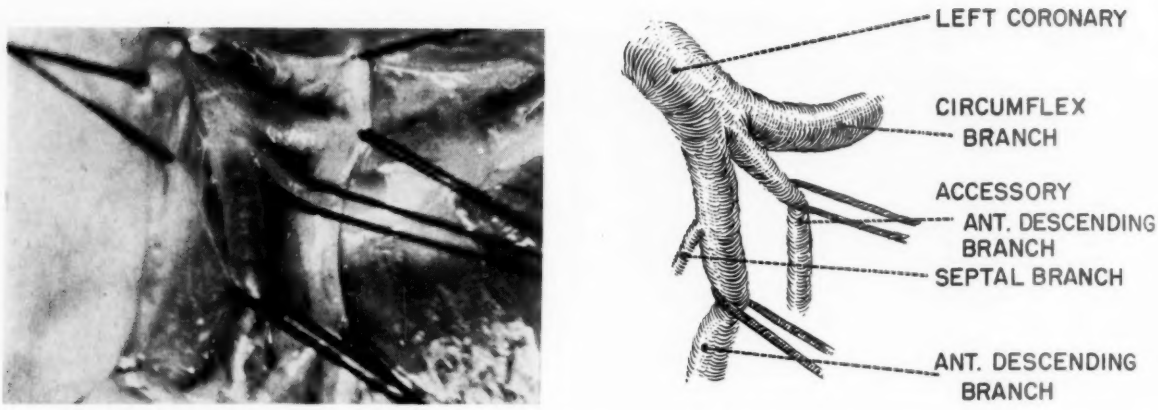

Fig. 3. The anterior descending branch and the septal branch can be seen. An accessory anterior descending branch is seen arising at the bifurcation of the left coronary artery.

branch of the left coronary artery indicate that this vessel is an excellent landmark for the duplication of the level of coronary obstruction in experimental studies. A technique has been presented and it is emphasized that adequate exposure during placement of the ligature is of prime importance in producing a standard result. By the use of this procedure, an attempt has been made to increase the validity of this method of evaluating the various techniques of myocardial revascularization.

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Sudden occlusion of the anterior tibial artery

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Sudden occlusion of the anterior tibial artery is a rare condition. McKechnie and Allen,[6] in reviewing 100 cases of sudden occlusion of the arteries of the extremities, reported 1 case due to thrombosis of the anterior tibial artery. Haimovici,[4] in a study of 330 cases of embolism to the extremities, found 9 due to occlusion of the anterior tibial artery, an incidence of 2.8 per cent. However, 4 of these showed no clinical manifestations except for absence of the dorsalis pedis pulse. Warren and Linton,[7] in examining 172 arterial emboli, did not find any which were exclusive to the anterior tibial artery. Most textbooks concerning peripheral vascular disease make little mention of this syndrome.

Only 12 cases of occlusion of the anterior tibial artery due to thrombosis or embolism have been previously described. Leriche,[5] in 1950, described 2 cases which he had seen among 2,000 cases of acute thrombosis. Two additional cases were described by Watson,[8] 3 by Albanese,[1] and 5 by Freedman and Knowles.[3] Six cases have been observed at the State University of Iowa Hospitals, 4 due to embolism, 1 to thrombosis and 1 to a gunshot wound of the leg (Table I). The importance of this syndrome lies in the fact that despite the presence of gangrene, proper treatment will frequently result in conservation of the extremity.

CASE REPORTS

Case 1. W. B., a 61-year-old white man, was admitted to University Hospitals on June 10, 1958, approximately 8 hours after he had experienced sudden severe pain, numbness, and coolness of the right lower extremity. Examination at the time of admission showed mild hypertension. Ice packs had been applied to the right lower leg and it was cold up to the midthigh region. No pulses could be palpated on the right side below the bifurcation of the aorta. All the pulses in the left lower extremity were present.

Shortly after admission, the patient was operated upon. The right common iliac artery was completely occluded by calcific atherosclerotic plaques with a soft clot distal to the occlusion. Thrombectomy, endarterectomy, and bilateral sympathectomy were performed. Postoperatively the man developed a 12 by 4 cm. area of gangrene over the midanterolateral aspect of the right leg and inability to dorsiflex the foot. The pulses in the right lower extremity remained absent. With prolonged conservative management, the area epithelized by September, 1959. The patient was then fitted with a Klenzak brace for his foot drop and was able to ambulate satisfactorily. He was last seen in February, 1960, at which time he was doing well.

Comment. The patient had developed a sudden thrombotic occlusion of the right common iliac and femoral vessels, which was treated by a thrombectomy and endarterectomy. The embolus to the anterior tibial artery probably originated from the iliofemoral thrombus. The patient's recovery was delayed by an ischemic ulcer over the proximal portion of the anterior tibial compartment, which finally epithelized. At the present time, he is walking well with an orthopedic brace.

Case 2. D. T., a 52-year-old white woman, was admitted to University Hospitals on Dec. 26, 1958. Two days prior to admission, while shopping, she had experienced a sudden sharp pain in her right calf which subsided after rest. A few hours later, while walking, she had again experienced a sharp pain in her right calf, which persisted until the time of admission.

Examination showed mitral stenosis and insufficiency and atrial fibrillation. There was a 3 by 4 cm. tender area with mild swelling, induration,

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and hypesthesia over the anterolateral aspect of the right leg. She was unable to dorsiflex the right foot. The popliteal and posterior tibial pulses were faintly palpable and the dorsalis pedis pulse was absent. The patient was treated with lumbar sympathetic blocks on several occasions with good results, and the tenderness gradually disappeared. She was discharged on Jan. 3, 1959.

The patient was last seen in May, 1959. On examination, signs were found of peripheral vascular insufficiency of the right foot. No pulses could be felt below the femoral artery. Dorsiflexion of the foot had returned to normal.

Comment. The patient had an embolus to the right anterior tibial artery, probably originating in the left atrium. The embolus caused spasm of the collateral vessels which was relieved by the paravertebral sympathetic blocks. The patient regained dorsiflexion of the foot, but suffers persistent changes of chronic peripheral arterial disease with atrophy of the skin, dependent rubor, and absence of pedal pulses. Haimovici[4] classified this condition as embolism with chronic postembolic ischemia. One of his cases of anterior tibial artery occlusion and one reported by Freedman and Knowles[3] were of this type.

Case 3. D. A., a 19-year-old white male, sustained an accidental gunshot wound of the right leg from a .22 caliber pistol on Dec. 9, 1956. The bullet, which had entered the leg posteriorly and lodged in the tibia, was removed in a local hospital and postoperatively the leg was placed in a cast. The patient did well until Jan. 3, 1957, when he began to bleed actively from the operative incision. After this bleeding episode, pulsations could no longer be palpated in the right foot and he was transferred to University Hospitals on January 15.

Examination showed a 2.5 by 3 cm. open wound over the anterolateral aspect of the right upper leg. The foot had good color and warmtn. The dorsalis pedis pulse was absent. The patient was unable to dorsiflex the foot. A femoral arteriogram showed filling of the posterior tibial artery but none of the anterior tibial artery.

The patient was operated upon on Jan. 17, 1957. The anterior necrotic area was débrided and contained approximately 300 to 400 c.c. of clotted blood. The popliteal artery was found to be ruptured. The posterior tibial artery was identified but the anterior tibial artery could not be found. A 5 cm. autogenous venograft was interposed between the popliteal and posterior tibial arteries with restoration of distal pulsations. The anterior tibial compartment was partially filled by implantation of the tibialis anticus muscle in the interosseous space and application of a skin graft over it. Examination of the débrided material showed an organized thrombus of the anterior tibial artery.

Postoperatively the toes of the right foot were cyanotic, cold, and numb. Lumbar sympathetic blocks were performed with good results and on January 21 a right lumbar sympathectomy was carried out with improvement in the color and temperature of the foot. Subsequently, the anterior tibial muscles became necrotic and it was necessary to débride the entire anterior tibial compartment. The defect was covered with split-thickness

Table I

Patient	*Etiology*	*Predisposing factors*	*Extent of gangrene*	*Surgical treatment*	*Factors leading to amputation*
W. B. (Case 1)	Embolus	Atherosclerotic occlusion of right common iliac artery	12 by 4 cm. area, mid-anterolateral aspect of right leg	None	—
D. T. (Case 2)	Embolus	Atrial fibrillation	None	None	—
D. A. (Case 3)	Gunshot wound	None	2.5 by 3 cm. open area, upper anterolateral aspect of right leg	Autogenous venograft, right popliteal artery; lumbar sympathectomy; débridement	—
H. Mc. (Case 4)	Embolus	Atrial fibrillation	Anterolateral aspect of right leg from 4 cm. below knee to 2 cm. above malleoli	Right supracondylar amputation	Gas gangrene, osteomyelitis of tibia
H. B. (Case 5)	Thrombus	Atherosclerosis	Toes of right foot	Amputation right leg below knee	Gangrene of foot
M. S. (Case 6)	Embolus	Atrial fibrillation	Right foot	Amputation right leg below knee	Gangrene of foot

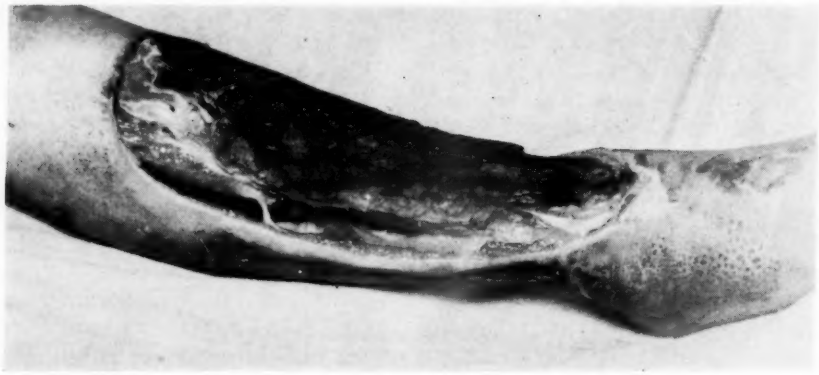

Fig. 1. Case 4. Right leg with area of gangrene over anterolateral aspect.

skin grafts and the patient discharged on March 10, 1957.

The patient was last seen in August, 1957. There was still a small defect in the superior portion of the wound but no evidence of osteomyelitis. There was hypesthesia over the sole of the foot and inability to dorsiflex the foot. The patient was able to walk satisfactorily with a Klenzak brace.

Comment. In this case, the patient had sustained a gunshot wound of the right leg with resultant partial destruction of the anterior tibial artery. The posterior tibial artery was severed but was anastomosed to the popliteal artery by means of an autogenous venous graft, which preserved circulation to the posterior aspect of the leg and the foot. Because of necrosis of the anterior tibial muscles, it was necessary to débride the anterior tibial compartment. Subsequently, the patient did well and he is now able to walk satisfactorily with a Klenzak brace.

Case 4. H. Mc., a 57-year-old white woman with a history of rheumatic fever and recent congestive heart failure, was admitted to University Hospitals on Feb. 26, 1945. On January 20 she had developed sudden pain, pallor, and coldness in the right leg. In spite of instructions by her local doctor, she had applied a heating pad to the leg. By the next morning there was a third degree burn over the anterolateral aspect of the leg. The patient was treated with heparin. Within 10 days the foot was normal and the blebs had disappeared. The muscles and overlying skin of the anterior tibial compartment were frankly gangrenous and the woman was transferred to University Hospitals.

Examination showed atrial fibrillation and slight cardiomegaly. Over the anterolateral aspect of the right leg, extending from 4 cm. below the knee to 2 cm. above the ankle, there was a large area of necrosis and gangrene involving the anterior tibial compartment (Fig. 1). The popliteal and posterior tibial pulses were present but the dorsalis pedis was absent. Dorsiflexion of the foot was absent. Roentgenograms of the right leg showed osteomyelitis involving the shaft of the right tibia and fibula with a considerable amount of gas in the soft tissues.

A supracondylar open amputation was performed on March 2. The postoperative course was uneventful and the patient was discharged on March 13, 1945.

Comment. In this case, pulsations were present in the popliteal and posterior tibial arteries and absent in the dorsalis pedis artery, indicating a block in the anterior tibial artery. The skin over the anterior aspect of the leg was burned and infection introduced. Because of the development of gas gangrene and osteomyelitis of the tibia, conservative management was contraindicated. A supracondylar amputation was performed and recovery was uneventful.

Case 5. H. B., a 74-year-old white man, was admitted to University Hospitals on June 22, 1959, because of an epidermoid carcinoma of the lower lip. Examination showed mild hypertension and occasional premature contractions. On June 26 a V excision and cheiloplasty were performed. Approximately 2 hours postoperatively the patient complained of sudden, severe pain in his right foot. On examination the foot was found to be white and cold with anesthesia up to the junction of the middle and lower thirds of the leg. The right popliteal pulse was present to 5 cm. below the knee. The pedal pulses were absent. Lumbar sympathetic blocks were performed on several occasions with no appreciable effect.

Examination the next morning showed tenderness and induration over the anterior tibial compartment with inability to dorsiflex the foot. There was decreased temperature over the distal third of the leg and foot and the distal half of the foot was mottled and violescent. A right lumbar sympathectomy was performed.

After this, the patient developed gangrene of the first 3 toes and amputation of the right leg

below the knee was performed on July 6. Examination by the pathologist revealed ischemic atrophy of the muscles of the anterior tibial compartment. There was a 4 cm. adherent thrombus of recent origin in the proximal portion of the anterior tibial artery. The posterior tibial artery was patent, but markedly narrowed. The patient's course after amputation was uneventful and he was discharged on July 16, 1959.

Comment. The patient probably had an acute arterial thrombosis of the right anterior tibial artery associated with arteriosclerosis obliterans. There was no obvious source for an embolus.

The patient was treated conservatively at first. The posterior tibial artery was markedly narrowed and the flow through it was inadequate to supply the foot, necessitating amputation below the knee. The presence of a thrombus in the anterior tibial artery was confirmed by the pathologist.

Case 6. M. S., a 40-year-old white woman, was admitted to University Hospitals on Nov. 30, 1954. Ten weeks prior to admission she had experienced a "heart attack" followed in 4 weeks by the sudden onset of pain, coldness, and numbness in the right foot and distal leg. The symptoms in the extremity had largely abated until 3 weeks prior to admission when she had experienced a serious exacerbation of symptoms.

Examination at the time of admission showed mitral stenosis and atrial fibrillation. There was gangrene of the right foot from the level of the malleoli distally. The right femoral and popliteal pulses were present.

On December 10 amputation of the right leg below the knee was performed. The anterior skin flap and muscle group had a poor blood supply. The posterior muscle group had a good blood supply. Examination of the specimen showed a 6 cm. area of anterior tibial artery and vein just above the malleoli to contain loose clot. Sections of this showed an adherent organizing thrombus. Sections through the posterior tibial and peroneal arteries showed no evidence of atherosclerosis, inflammatory change, or occlusion.

On December 20 a mitral valvuloplasty was attempted but the patient died on the operating table. On postmortem examination numerous emboli were found from the left auricle to the left ventricle and throughout the abdominal portion of the aorta and its bifurcation. There was an organizing thrombus in the right common iliac artery.

Comment. This case is extraordinary in that the usual signs and symptoms of occlusion of the anterior tibial artery were not present. In this syndrome the foot is spared because the lateral plantar artery which forms the deep plantar arch arises as one of the terminal branches of the posterior tibial artery. At the time of amputation, the operator commented on the poor blood supply of the anterior muscle group as compared with the posterior. This was confirmed by the finding of a clot in the distal anterior tibial artery. The posterior tibial and peroneal arteries were normal both grossly and microscopically. This patient possibly had an anomalous arterial blood supply to the foot which would account for the distribution of the gangrene.

DISCUSSION

The clinical features which compose the anterior tibial artery syndrome include (1) sudden excruciating pain over the anterior muscle compartment of the leg, (2) muscular edema, induration, and tenderness on palpation, (3) a reddish-purple discoloration of the overlying skin, (4) inability of the patient to stand, walk, or dorsiflex the foot or toes and (5) absence of the dorsalis pedis pulse. Freedman and Knowles[3] also include cutaneous anesthesia of the first interdigital cleft due to ischemic neuropathy of the anterior tibial nerve.

The anterior tibial compartment is bounded by the tibia, interosseous membrane, fibula, and the overlying fascia. It contains the tibialis anticus, extensor hallucis longus, and extensor digitorum longus muscles, the anterior tibial artery and veins, and the deep peroneal nerve. Blomfield[2] studied the arterial blood supply of these muscles by the injection of radiopaque media into the main limb vessels of cadavers, dissecting out the individual muscles and making roentgenograms. The tibialis anticus receives its entire blood supply from the anterior tibial artery by a series of anastomotic loops. The extensor digitorum longus and the extensor hallucis longus also receive an abundant blood supply from perforating vessels from the posterior tibial and peroneal arteries which pass through the interosseous membrane from the posterior compartment of the leg. However, the intramuscular anastomoses are much finer and less efficient in the extensor hallucis longus than in the extensor digitorum longus. Sudden occlusion of the anterior tibial artery at its proximal end would deprive the tibialis anticus of its entire blood supply and result in total necrosis of this muscle. The extensor digitorum longus and extensor hallucis longus would

be less affected because of their additional blood supply by perforating vessels from the posterior compartment. The extensor hallucis longus would sustain greater damage because of its less efficient intramuscular anastomotic network.

The extent of infarction after occlusion of an artery by an embolus or thrombus is dependent upon the site and extent of the occlusion, as well as the degree of vasospasm, secondary thrombosis, and impairment of the collateral circulation by atherosclerosis. Swelling in the anterior tibial compartment after occlusion of the anterior tibial artery tends to obliterate the collateral circulation and increase the amount of muscle necrosis. The success of conservative treatment is dependent on the sufficiency of anastomotic channels and the absence of complicating factors such as infection.

Proper management of this condition depends upon early diagnosis. With appropriate treatment, in most cases, the leg can be preserved and amputation avoided. Elevation of the extremity and extremes of temperature are to be condemned. Failure of the patient in Case 4 to heed her physician's advice was the probable cause of gangrene and the eventual loss of the extremity.

Relief of vasospasm may be attempted by the use of vasodilator drugs such as papaverine, lumbar paravertebral sympathetic block, or lumbar sympathectomy. The effect of sympathetic block on muscle circulation is still questionable. In Case 2 paravertebral sympathetic block was performed on 2 occasions. The patient subsequently had return of dorsiflexion of the foot. Lumbar sympathectomy was performed in Case 3 with good results. Both paravertebral sympathetic blocks and lumbar sympathectomy were performed in Case 5 with no significant improvement.

Anticoagulants may be helpful in preventing secondary thrombosis. Attempts at dissolving thrombi have been made recently with human fibrinolysin. Experience with this agent is limited and its evaluation will have to await more results. Embolectomy is probably of little value.

If the patient is seen within 12 hours after onset, fasciotomy may help relieve pressure in the closed anatomic compartment. Fasciotomy performed after necrosis has occurred is apt to favor the development of gas gangrene. In the presence of infection or gangrene, débridement of the anterior tibial compartment should be carried out. Subsequently, the patient should be fitted with a foot-elevating spring brace for ambulation. Débridement was performed in Case 3, Leriche's[5] 2 cases and Albanese's[1] 3 cases with good results. Amputation was necessary in 1 of our cases because of osteomyelitis and in 2 others because of inadequate circulation to the foot.

SUMMARY

1. Six cases of occlusion of the anterior tibial artery are reported, of which 4 were due to embolism, 1 to thrombosis, and 1 to a gunshot wound.

2. The clinical features of the anterior tibial artery syndrome are described.

3. The vascular pattern of the anterior tibial muscles is discussed.

4. Treatment is outlined and the importance of conservative management is stressed.

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Injuries of the vena cava caused by external trauma

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Accidental lacerations of the vena cava inflicted during operation for diseases of the cardiopulmonary, urogenital, and peripheral vascular systems are not uncommon, and repair of such injuries is usually accomplished without difficulty and without harmful effect on the patient. Lacerations of the vena cava which result from external trauma, although relatively rare, usually result in death. Their critical nature is due to difficulty in diagnosis, delay in treatment, number and extent of associated injuries, technical problems encountered in repairing such injuries, and lack of information regarding ideal therapy of the venous injury itself.

Only 22 successfully treated patients with vena caval injuries are mentioned in the literature, 19 with injury of the inferior vena cava and 3 with injury of the superior vena cava.[1-6, 8, 9, 11, 12, 14, 15, 17, 18, 22-24] Moreover, except for one report of 3 cases, the reports are of single cases, which indicates the general lack of individual experience with this problem. The purpose of this report is to present an analysis of a relatively large number of injuries seen in a single hospital, because such an analysis both emphasizes the problems encountered and indicates certain therapeutic measures that may increase the incidence of survival.

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CLINICAL MATERIAL

The majority of patients who survive violent trauma in the Houston area are admitted to the Jefferson Davis Hospital for definitive treatment, and most patients who die from violent trauma, either before or after hospital admission, are routinely submitted for autopsy by the county pathologist to determine the cause of death. The available autopsy records of the county pathologist and the clinical hospital records of all patients with vena caval injuries during the past 14 years were reviewed and analyzed in order to appraise the total problem imposed by this type of injury. There were 85 patients in this series, 46 (55 per cent) who died before admission and 39 (45 per cent) who survived to reach the hospital (Table I). The ages of the patients ranged from 15 to 56 years; however, 90 per cent were between 15 and 40 years of age. There were 68 men and 17 women in the series. The general health of the patient had been good until the time of injury in almost every case.

Location and type of injury. The caval injury was located in the extrapericardial segment of the superior vena cava in 27 patients (31 per cent), 25 of whom were dead on admission. The injuries in the latter instances resulted from gunshot wound in 18, stab wound (knife) in 4, and crush injury in 3 (Table I). Death was due to hemorrhage from both the caval wound and as-

Table I. *Location and type of vena caval injury in 84 patients*

Location and type of injury	*Alive on admission*	*Dead on admission*
Superior vena cava	2	25
Gunshot	1	18
Stab	1	4
Crush	0	3
Inferior vena cava	37	21
Gunshot	29	18
Stab	7	3
Crush	1	0
Totals	39	46

Table II. *Associated injuries in patients admitted to hospital with vena caval injury*

	Superior vena cava		*Inferior vena cava*	
Organ	*Alive (2 patients)*	*Dead (23 patients)*	*Alive (37 patients)*	*Dead (21 patients)*
Internal mammary artery	1	1		
Lung	2	21	2	3
Major pulmonary vessel		11		1
Innominate vein		2		
Heart		6	1	23
Aorta, thoracic		5		
Aorta, abdominal			5	9
Liver		3	17	12
Spleen			2	1
Kidney			2	2
Pancreas			6	2
Stomach			5	1
Colon			15	7
Small intestine			23	9
Portal vein			3	3

Table III. *Level of injury in 37 patients admitted alive with injury of the inferior vena cava and results of treatment*

Location	*Survived*	*Died*
Above diaphragm	2	—
Between renal veins and diaphragm	—	4
Level of renal veins	4	4
Between renal veins and bifurcation	7	7
At bifurcation of vena cava	3	6
Totals	16	21

sociated injuries of the heart, thoracic aorta, and major pulmonary vessels (Table II). Only 2 patients with injury of the superior vena cava survived to reach the hospital, and 1 died almost immediately after admission to the emergency room. The injury in this case had been caused by a knife, which had transected the right internal mammary artery and had produced a large laceration of the extrapericardial segment of the superior vena cava. This patient was moribund at the time of admission and died from hemorrhage before effective therapy could be instituted. The second patient had sustained a through-and-through penetrating bullet wound of the extrapericardial segment of the vena cava. Although this patient was also in profound shock at the time of admission, he lived to be treated.

Inferior vena caval injury was present in 58 patients (69 per cent), 21 (36 per cent) of whom were dead on arrival and 37 (64 per cent) of whom survived injury and were admitted alive to the hospital. The method of injury in these cases was gunshot wound in 47, stab wound (knife) in 10, and crush injury in 1 (Table I). The ratio of the various types of injuries was essentially the same regardless of whether the patient was dead or alive at the time of admission. The precise level of inferior vena caval injury could not be determined from the autopsy records of the patients who were dead on admission; however, all patients admitted alive underwent operation and the level of injury was precisely recorded in every case. The location of injury in the latter 37 cases was above the diaphragm in 2, between the renal veins and the diaphragm in 4, at the level of the renal veins in 8, between the renal veins and the bifurcation of the vena cava in 14, and at the bifurcation in 9 patients (Fig. 1 and Table III). The injury or laceration in most of the latter cases extended down into one or both common iliac veins. The presence of continued hemorrhage or active bleeding from the vena caval laceration at the time of operation was dependent upon the location of the injury. The vena caval laceration had become

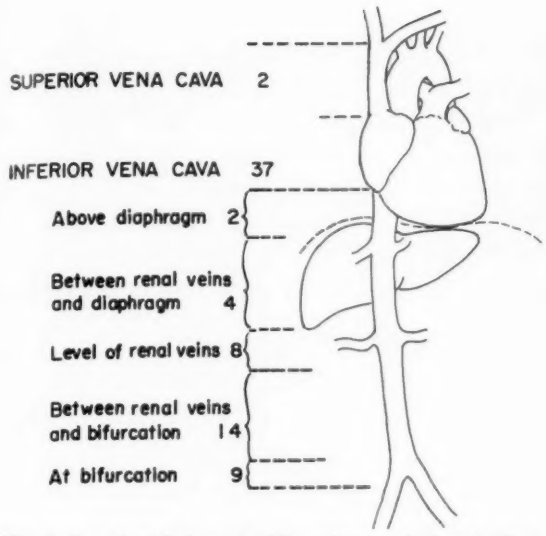
SUPERIOR VENA CAVA 2
INFERIOR VENA CAVA 37
Above diaphragm 2
Between renal veins and diaphragm 4
Level of renal veins 8
Between renal veins and bifurcation 14
At bifurcation 9

Fig. 1. Level of injury in 39 patients admitted alive with injury to the vena cava.

occluded with thrombus and active bleeding had stopped in 2 patients (100 per cent) with injury above the diaphragm, 2 patients (50 per cent) with injury between the diaphragm and the renal veins, 5 patients (62 per cent) with injury at the level of the renal veins, 7 patients (50 per cent) with injury between the renal veins and the bifurcation of the vena cava, and 1 patient (11 per cent) with injury at the bifurcation of the vena cava.

Associated injuries. The vena cava is protected from behind by the vertebral column; consequently, most injuries to it result from anterior or lateral penetrating wounds. Because of its posterior and central location, other organs are usually penetrated by the same implement which produces injury to the vena cava. Thus, in this series of cases, every vena caval injury was complicated by one or more injuries of other visceral organs (Tables II and IV). Because of the proximity of the vena cava to the aorta, heart, lung, and major pulmonary vessels in the chest, and to the aorta, mesenteric vessels, portal vein, liver, pancreas, and bowel in the abdomen, these were the organs most frequently involved. The nature and extent of the associated injuries assumed major importance both in prognosis and in problems of therapy. All patients with superior vena caval injuries had associated injury of one or more major vascular structures, usually the heart, thoracic aorta, pulmonary vessels, and lung, and all of these patients, except one, died of hemorrhage either before or at the time of admission to the hospital. All patients with inferior vena caval injuries who died before admission to the hospital had associated lacerations of the abdominal aorta, liver, and heart. Death in these cases was obviously from rapid, massive hemorrhage. Patients with inferior vena caval injury who were admitted alive had injury of the abdominal aorta in 5 (14 per cent), liver in 17 (46 per cent), spleen in 2, kidney in 2, pancreas in 6, stomach in 5, colon in 15 (40 per cent), small intestine in 23 (62 per cent), and portal vein in 3 (Tables II and IV). Treatment in these cases required control not only of the vena caval injury but repair of the injuries to the aorta, severely lacerated liver, spleen, pancreas, kidney, stomach, colon, and small intestine. These injuries were frequently associated with massive hemorrhage which was difficult to control, and of the 30 patients treated during the past 5 years the 14 who died had associated injury of the liver, aorta, or iliac artery. Death in most of these cases occurred during operation because of inability to control hemorrhage.

Table IV. *Associated injuries in 30 patients with inferior vena caval injury treated since 1954**

	Successful treatment (16 patients)		*Deaths (14 patients)*	
Injury	*No.*	*%*	*No.*	*%*
Heart	1	6	—	—
Aorta	—	—	5	36
Iliac artery	—	—	2	14
Liver	8	50	8	57
Portal vein	—	—	3	21
Hepatic artery	—	—	1	7
Small bowel	8	50	9	64
Colon	6	37	6	43
Pancreas	3	19	3	21
Stomach	3	19	2	14

*Comparison of nature and incidence of injuries in patients who survived with those in patients who died.

Condition of patient on admission and at time of operation. Most patients were admitted to the hospital within 1 hour of injury; however, only 2 patients (7 per cent) with superior vena caval injury, and 37 patients (64 per cent) with inferior vena caval injury were alive on admission. Both of the former patients were in profound shock, and one died at the time of admission before therapy could be started. The second patient continued to show signs of shock and blood loss in the chest despite blood transfusions until bleeding was controlled by operation. Of the latter patients, 30 (81 per cent) showed signs of severe blood loss (pallor, sweating, profound hypotension, tachycardia, and distant heart sounds). Only 7 of these patients entered the hospital with normal and stable vital signs. The extent of blood loss both before and after admission is evidenced by the fact that 195,815 ml. of blood was administered to the 38 patients treated, an average of 5,126 ml. for each patient. Despite the liberal use of whole blood before operation 21 (67 per cent) of the 31 patients admitted in shock and treated continued to exhibit signs of continuous blood loss. Active bleeding was present in the region of vena caval injury in all 21 patients in whom the vital signs could not be restored and maintained at normal levels by whole blood transfusion before operation. Bleeding had, however, been controlled by the tamponade effect of a retroperitoneal or mediastinal hematoma in the 17 patients (46 per cent) with normal and stable vital signs at the time of abdominal operation for inferior vena caval injury.

Treatment. Matched or low titer type O Rh negative whole blood was administered by cannula in all instances. In 2 of the earlier patients with inferior vena caval injury, blood was transfused into the saphenous vein. Blood administered by this route was not only ineffective but increased the caval bleeding and contributed to the difficulties of repair. Because of this experience, patients with penetrating abdominal injury subsequently were given blood through one or more veins in the upper extremities. Conversely, in patients with thoracic injury, transfusions were administered through veins of the lower extremities.

Water-seal drainage through an intercostally placed tube was quickly instituted in the patient with superior vena caval injury who survived to be treated. Major chest wall or intrathoracic vascular injury was evidenced by continued blood loss through the tube and hypotension which persisted despite transfusion therapy. Operation to control hemorrhage was quickly performed. The right side of the chest was explored through the fifth intercostal space. A through-and-through penetrating bullet wound of the superior vena cava was found just proximal to the bifurcation into the innominate veins. Proximal and distal control of bleeding was obtained with arterial clamps and the wounds were repaired by single over-and-over suture with fine arterial silk.

All of the patients with inferior vena caval injury showed signs of intra-abdominal injury at the time of admission, and the need for abdominal operation was obvious. Operation was therefore begun within 1 hour in most instances, and always within 2 hours. Early operation was indicated in most cases as part of the resuscitative treatment to control massive, continued blood loss. As previously indicated, multiple injuries were present and the majority were associated with hemorrhage. The first objective of operation was control of hemorrhage and the second or final objective was repair of injury. For this reason, bleeding lesions were treated first and such lesions as laceration of the gastrointestinal tract were treated last by appropriate suture, local excision and end-to-end anastomosis, or exteriorization. The order of repair was therefore dependent upon the degree of bleeding and its ease of control. As a rule, injuries with bleeding which could be easily and more completely controlled by packing with gauze sponges or other simple methods were repaired after the injuries with the most vigorous bleeding had been repaired.

The operative procedure employed in the treatment of the vena caval injury depended

upon a variety of factors, including period of surgical advancement, the location of injury, the extent of injury, and the condition of the patient. Of the patients who underwent operation prior to 1955, 3 were treated by ligation, 2 by suture, and 2 by packing with gauze. The gauze pack in one case was left in place as the permanent method of controlling hemorrhage and was removed later. After 1955, largely as a result of increasing experience of the resident staff in the principles and techniques of vascular surgery, the caval injury was repaired by suture whenever possible. This method of repair was considered essential in all patients with injury at or above the level of the renal veins. Injuries below the renal vein were treated by suture repair unless a sizable defect existed or the condition of the patient necessitated a quicker operation. In the latter cases, the vena cava was ligated proximal and distal to the injury. The lumbar veins entering the injured segment were ligated separately. Thus, in 30 patients who underwent operation during this period, the caval injury was sutured in 17 (56 per cent). Injury was above the diaphragm in 2, at the renal veins in 6, and below the renal veins in 9. The vena cava was ligated in 8 patients with injury below the level of the renal veins. In 4 patients, the vena cava was injured in the region of the hepatic or portal veins and was associated with massive liver wounds. The profuse hemorrhage associated with these wounds could not be controlled in any way, including packing, and the patients died during operation. The vena caval injury located below the renal veins was packed during attempts to control hemorrhage from a large stellate laceration of the liver in one patient who sustained injury of the liver, vena cava, urinary bladder, and pelvis from a crush injury. The patient died from hemorrhage before the bleeding could be controlled in the liver.

RESULTS

The single patient with superior vena caval injury in whom treatment was possible survived injury and operative repair and left the hospital in good condition. Of the 37 patients with injury of the inferior vena cava alive on admission, 16 (43 per cent) survived. Survival in the latter cases was dependent upon a number of factors including date of injury, condition of patient at the time of operation, the presence of bleeding at the site of caval injury at the time of operation, the location of injury, and the location and extent of associated injury. All 7 patients studied who had been treated prior to 1955 died, and 16 (53 per cent) of the 30 patients treated since that time survived. Of the 17 patients whose vital signs were essentially normal at the time of operation and in whom the vena caval wound had become occluded by thrombus which caused cessation of active hemorrhage, 14 patients (82 per cent) survived. Only 2 patients survived (10 per cent) of the 20 who continued to show signs of massive blood loss despite vigorous transfusion therapy. The presence of active bleeding at the site of caval injury, and hence survival of the patient, was dependent upon the level of injury. Because of the tamponading effect of a hematoma trapped in the mediastinum and retroperitoneal tissues, bleeding had stopped in 2 patients with injury above the diaphragm, both of whom survived; 5 patients with injury at the level of the renal arteries, 4 of whom survived; 7 patients with injury between the renal arteries and bifurcation of the vena cava, all of whom survived; and 1 patient with injury at the bifurcation, who survived. Only 2 patients lived in whom active bleeding was present and these patients had injury of the vena cava in the region of the bifurcation. Despite the fact that bleeding had stopped before operation in 2 cases, all 4 patients with injury of the vena cava between the diaphragm and renal veins died. One patient with injury at the level of the renal veins died although bleeding had stopped before operation.

Survival was particularly related to the type of procedure employed in the treatment of the caval wound. All patients in whom packs were used died. Packs were used as a permanent form of therapy in only 1

patient, who died 1 hour after operation. In the other patients in whom this method was employed, packs were inserted as a desperate means of controlling bleeding to afford proper exposure for vena caval repair or ligation. Unfortunately, this and all other attempts at controlling hemorrhage were unsuccessful in these cases, and the patients died during operation. Ligation seemed as effective in the control of hemorrhage and survival of the patient as local repair when employed under similar circumstances. Pulmonary embolism, thrombophlebitis, and leg swelling did not occur after either procedure.

The cause of death in the 21 patients with inferior vena caval injury who died after admission to the hospital was uncontrolled hemorrhage in 15 (71 per cent), renal failure in 2 (9 per cent), peritonitis in 1, and causes unknown but probably related to severe blood loss before control of hemorrhage in 3. Of the 15 patients who died of uncontrolled hemorrhage, 12 patients died during operation, and in most instances hemorrhage occurred both from the vena caval wound and from wounds of the aorta, liver, portal vein, iliac artery, and hepatic artery. During the period before 1955, 3 patients died from continued hemorrhage from the vena caval wound during the first 12 hours after operation. The injury was treated by packing in 1, suture in 1, and ligation in 1. Despite the frequency of colon, stomach, and small bowel injuries, only 1 patient died from peritonitis and was one of the earlier patients in the series.

The principal factor determining survival was associated injury. With the exception of 6 patients treated prior to 1955, all deaths were directly or indirectly related to the problem of massive hemorrhage resulting to a large extent from associated injury. A comparison of associated injury in patients who survived with that in patients who died after admission to the hospital indicates that injuries of the aorta, iliac arteries, hepatic artery, and portal vein were present in 70.1 per cent of the patients who died, whereas no patient survived with these injuries when they were associated with injury of the vena cava (Table IV). The incidence of liver, small bowel, colon, stomach, and pancreatic injury was essentially the same in the 2 groups, and with the exception of liver damage, these injuries were not a significant factor in the survival of the patient. Liver injury was usually more extensive in the patients who died and was the factor leading to death in most patients who did not have concomitant injury of the aorta, iliac arteries, portal vein, and hepatic artery. Serious associated injury of vital structures, however, did not preclude survival, as demonstrated by the following report concerning a patient with injury of the heart and the inferior vena cava above the diaphragm.

CASE REPORT

A 39-year-old Negro man had received a through-and-through gunshot wound of the low midchest approximately 1 hour before admission. The patient developed cardiac arrest and cessation of respiration at about the time of admission to the emergency room. The left side of the chest and pericardium were immediately opened. A large blood clot was removed from the pericardium, and the heart was found to be in standstill. Cardiac massage was begun and normal heart action was immediately restored. With the restoration of normal heart action and reasonably normal vital signs, bleeding resumed from the pericardial incision. The patient was transferred to the operating room and after the chest wall incision had been extended into the right side of the chest, the pericardium was opened, widely exposing the bullet wounds. The bullet had entered the anterior wall of the right atrium and exited through the posterior wall of the intrapericardial segment of the inferior vena cava. Bleeding was first controlled by digital pressure and then with partial occlusion clamps. The lacerations were repaired with continuous through-and-through arterial suture and the wound was closed. The patient had an uneventful postoperative course and was discharged from the hospital 10 days after injury.

DISCUSSION

Vena caval injury either by blunt or penetrating trauma is a very serious injury, with death occurring before admission to the hospital in over 50 per cent of the cases. Because of life-endangering hemorrhage which results both from the caval injury and

the associated injuries of other vascular organs, and because of the problems imposed by repair of these injuries, death is still frequent after admission despite application of the total services of a hospital accustomed to handling vascular emergencies. Thus, during the past 4½ years, only 17 patients (55 per cent) survived of the 31 patients admitted to the Jefferson Davis Hospital. These results will, of course, improve with increasing experience with vascular injuries, as indicated by the fact that all the survivals in this series occurred during the 4½ years. However, significant improvement may occur as a result of some change in the approach to the problem. The ideal solution is social, economic, and legal in nature and is beyond the scope of this presentation. The avenues of change open to the surgeon are (1) earlier operation and (2) the development of easier and safer techniques of treating the injury. With regard to the former possibility, it should be recognized that vena caval injury may be a part of any intra-abdominal or intrathoracic injury, and in the presence of continued hemorrhage, immediate operation should be undertaken with massive whole blood transfusions. With regard to the second possibility, it should be recognized that packing of vena caval injuries is extremely uncertain in the control of hemorrhage, and in view of the poor results we have had with this method of therapy, we believe that it should never be considered as a means of definitive treatment. Suture repair or ligation is the preferable method of therapy in most cases in which active bleeding is encountered at operation. For injuries below the renal veins, no significant difference exists in the results obtained by either of these methods in terms of survival, embolic phenomenon, phlebitis, or leg swelling. Of these procedures, the simplest or easiest to apply should be selected. Traumatic lesions at or above the renal veins should be repaired and caval continuity maintained because laboratory and clinical evidence indicates that acute sudden occlusion at this level is incompatible with survival in most cases.[10, 13, 16, 19-21] Repair may be accomplished either by direct suture of opposing wound edges or, in the presence of a defect, by insertion of a patch graft sutured circumferentially to the wound edges. Large defects may be closed by tubular grafts. However, the need for this method of treatment is theoretical in nature because patients with injuries which produce such a defect, in our experience, do not live to reach the hospital. Moreover, tubular grafts in the inferior vena cava fail from thrombosis early after operation in most cases.[17]

The most significant finding contributing to survival of the patient was the absence of active bleeding in the region of caval injury. Most patients in whom bleeding was active at the time of operation were in poor general condition at the time of admission and at the time of operation despite vigorous transfusion therapy. Most of these patients died during operation from hemorrhage resulting from the vena caval wound and from associated injuries of the aorta, iliac arteries, and other vascular organs. Most patients in whom bleeding had stopped before operation were in good general condition and survived the injury and operation. The notable exceptions occurred in patients in whom the retroperitoneal hematoma was explored, which caused return of vigorous bleeding after nearly fatal hemorrhage had been controlled elsewhere. Of the 3 patients in whom this occurred, the injury was located above the renal veins under the liver in 2 and at the level of the renal veins in 1. Considering the low pressure within the vena cava and its tributaries and the difficulties of exposure, and in view of our other experience, we have recently avoided exploration of nonpulsating retroperitoneal hematomas in the absence of active bleeding. For example, such hematomas almost certainly representing vena caval injury have been found behind and below the liver above the renal veins in 3 patients during the past 2 years. The associated injuries of the liver, colon, and small intestine were repaired and the retroperitoneal hematoma was not disturbed. All of these patients survived in

contrast to the 4 patients in this series in whom an attempt was made to repair the caval injury at this level, including 2 patients in whom active bleeding had stopped before operation. The patients in whom the hematoma was not explored are not included in this study because vena caval injury was not definitely confirmed. The duodenum and pancreas may also be injured at this level and serious complications, or even death, may occur if these injuries are not repaired. To exclude the possibility of injury of these organs, exploration of the hematoma may be required. The decision depends upon the risks of fatal hemorrhage from the vena cava and upon the possibilities of injury to these organs and the severity of complications which may result from lack of repair. In our experience occult duodenal injury is rare in patients who live to reach the hospital. For these reasons it would appear advisable not to open the hematoma unless indications of duodenal injury were obvious.

SUMMARY

There were 85 patients in this series of cases, 68 men and 17 women between the ages of fifteen and fifty-six years. The caval injury was located in the superior vena cava in 27 patients, 18 of whom were injured by gunshot wound, 5 by stab wound, and 3 by crush injury. The remaining 58 patients had injury located in the inferior vena cava, produced by gunshot in 47, stab wound in 10, and crush injury in 1.

Only 2 patients (7 per cent) with superior vena caval and 37 patients (64 per cent) with inferior vena caval injury survived to be admitted to the hospital. One of the former patients was moribund and died immediately upon admission. All of the remaining patients except 7 with inferior vena caval wounds were in profound shock at the time of admission because of hemorrhage from both the caval wound and secondary organ injuries which were present in every case. Early operation within 1 to 2 hours was carried out in each case. The single patient with superior vena caval injury who underwent operation and 16 (43 per cent) of the 37 patients with inferior vena caval injuries who underwent operation lived and left the hospital in good condition.

Death in these cases was related primarily to secondary organ injury. For example, a major vascular injury of the aorta, iliac artery, portal vein, or liver was present in essentially every patient who died. On the other hand, the presence of this type of lesion did not prevent survival in some cases.

The most effective method of treating the caval injury varies with the presence of bleeding and the location and extent of injury. Hematomas surrounding a caval injury which has stopped bleeding should neither be explored nor repaired, particularly when the laceration is located in an inaccessible area, such as beneath the liver.

All lacerations associated with continued hemorrhage should be repaired, and the preferable method depends upon the location and extent of injury. All lacerations at and above the level of the renal veins should be repaired and venous flow maintained. Patients with these lesions who live to reach the hospital usually have small lacerations which can be repaired by direct suture or by the insertion of patch grafts. Lacerations of the inferior vena cava below the renal vein have, in our experience, been repaired or ligated with equal effectiveness in terms of survival and late complications.

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Pediatric surgery

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Surgical management of extensive hemangioma associated with severe hemorrhage in an infant: case report

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Small hemangiomas are relatively common lesions in infants and children. Treatment of these varies from mere observation to simple surgical excision. Other modalities commonly employed include freezing necrosis or thrombosis, implantation or surface application of radium, roentgen radiation, and sclerosis by means of a variety of chemical irritants.

Large hemangiomas are more unusual and, depending on their size, location, and vascularity, may be the source of severe hemorrhage or extensive tissue destruction. Under these circumstances, surgical excision may become mandatory. The following case report describes a patient with an extensive cavernous hemangioma involving the entire perineum. The lesion was the source of repeated episodes of serious bleeding which eventually precluded any form of therapy other than radical surgical removal.

CASE REPORT

M. V., a 5½-month-old, well-developed white female infant, was first admitted to St. Luke's Hospital in April, 1959. A large, bulky, cavernous hemangioma occupying the perineum and a portion of the buttocks had been noted at birth. Bleeding from the mass was first observed by the family physician when the child was 2 weeks old. In December, 1958, at age 1 month, the patient had been hospitalized at another institution. During that admission she had received 2 transfusions because of blood loss from the lesion. In addition, radiation therapy of the tumor was instituted. This consisted of 400 r (in air) on 100 kv. through a 6 by 6 cm. port, tangentially administered to the perineum in January, 1959, and 600 r (in air) on 100 kv. in divided doses to the anterior and posterior perineum through a 6 by 6 cm. port in March, 1959.

On admission to our hospital, physical examination showed the patient to be a well-nourished infant, normal in all respects except for a large fungating perineal mass which measured 14 by 8 by 7 cm. The tumor occupied all of the perineum and a portion of the buttocks, including the vaginal and anal orifices. It appeared to extend into the anus for a short distance and occupied both labia minora and majora (Fig. 1). The tumor mass was firm and rubbery in consistency and slightly compressible. The surface appeared intact but there was bleeding noted from the area of the lesion adjacent to the anus. The hemorrhage from this region was severe enough to necessitate 5 transfusions of 100 to 200 ml. of whole blood each in the first week of hospitalization.

Because of the size and vascularity of the tumor, it was believed at first that surgical excision would be too hazardous in an infant of 5½ months. Consequently, further roentgen radiation amounting to 112 r (in air) on 140 kv. was given to the tumor surface through two 7 cm. ports directed tangentially. On the fifth hospital day, a sigmoid loop colostomy was performed in an attempt to reduce trauma and continued ulceration of the hemangioma, particularly where the growth encroached on the anus. At this time 3 small hemangiomas were removed from the right forearm, left axilla, and right ear without event. The latter were diagnosed microscopically as hemangiomas of the mixed type.

Episodic bleeding from the tumor continued for several weeks after the colostomy had been performed. This was controlled adequately with pressure dressings, although 5 additional transfusions

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Fig. 1. Cavernous hemangioma arising from perineum. Lesion completely encompasses the anal and vaginal orifices. Superficial ulceration can be noted in portion of the tumor adjacent to the anus. Sigmoid colostomy had been performed 10 days previously.

of 150 to 200 ml. each were required during the 8 days after operation.

During the next 3 months, bleeding was noted only infrequently. In July, 1959, 4 months after admission, daily injections of 5 ml. of Sodium Sotradecol were instilled around the periphery of the lesion. These were continued at weekly intervals in the outpatient department after the child had been discharged from the hospital on July 17, 1959. Despite this therapy, however, there was no appreciable decrease in the size or vascularity of the mass. Intermittent bleeding was noted again in October, 1959, and the child was readmitted to the hospital. After a severe hemorrhage from the anal portion of the tumor, requiring 150 ml. of whole blood shortly after the second admission to our hospital, it was deemed necessary to attempt surgical removal of the lesion. This was undertaken on Nov. 10, 1959. The hemangioma was mobilized anteriorly and a small rim of normal skin was removed with the tumor. It was dissected free from the labia and the perineal muscles. Very large venous channels measuring up to 1 cm. in diameter were encountered in the subcutaneous tissues entering the hemangioma through the perineal musculature. There were areas of the tumor in which the bleeding appeared arterial. The procedure was arbitrarily terminated after 2 hours of dissection and it was decided to complete the removal at a second stage. At this time, approximately one-half of the tumor had been mobilized from the subcutaneous tissue and the perineal structures. Blood loss during the procedure, despite meticulous attention to hemostasis, was measured at 610 ml., or approximately 75 per cent of the infant's total normal expected blood volume of 806 ml., as calculated preoperatively by radioactive serum albumin. Even with accurate blood replacement it seemed expedient to leave the partially mobilized and devascularized tumor in situ and resuture the skin margins to the perineal skin. This was done and despite an additional blood loss of 810 ml. in the 48-hour period after the operation, the baby withstood the procedure very well. Blood loss during the operation and postoperatively thus totalled 1,420 ml. This was accurately replaced as verified by postoperative blood volume studies. On Nov. 20, 1959, after a 10-day interim, complete excision of the lesion was accomplished. It was apparent at this stage that a significant portion of the external anal sphincter musculature had to be sacrificed in order to properly encompass the lesion (Fig. 2). Despite tedious, careful hemostasis, blood loss during the second procedure totalled 2,000 ml. with an additional 1,280 ml. being required during the succeeding 2 days. Thus, 3,280 ml. of blood were required after the second stage to maintain a calculated blood volume of 920 ml. The 2 procedures necessitated the replacement of 5,700 ml. of blood, or approximately 6½ times the infant's normal total blood volume. The patient recovered well and in spite of an extensive granulating wound, the large defect rapidly healed. The healing process was aided by enzymatic débridement with streptokinase-streptodornase on the fifteenth and sixteenth days after the second operation. Epithelization of the granulating surface was hastened by the insertion of skin graft "buds" directly into the granulation tissue on the eighteenth day after complete excision of the tumor.

Pathologic examination confirmed the diagnosis of a cavernous hemangioma. Grossly the tumor was trabeculated, soft, and contained many large

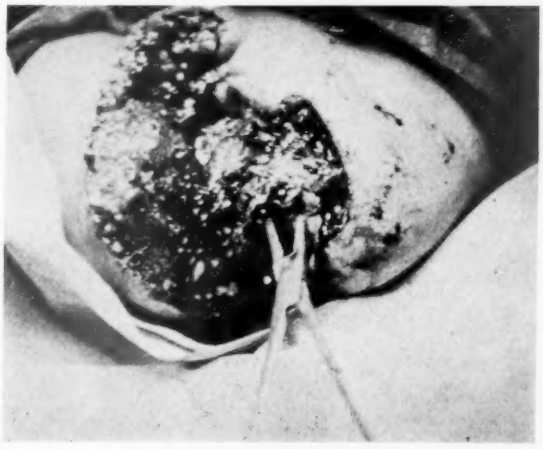

Fig. 2. Operative wound after complete removal of the hemangioma. The instrument indicates the anal orifice which was completely encircled by the tumor. The vaginal orifice and labia majora can be noted at the top of the operative area.

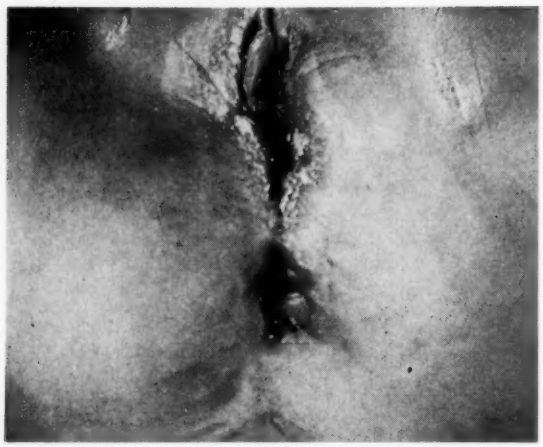

Fig. 3. A close-up view of the operative field, 8 months after surgical removal of the large hemangioma. The vaginal orifice is at the top of the picture. The anal opening and anal mucosa can be noted below. No stenosis has occurred to date.

venous channels. Some thrombosis was noted in a few of the sinusoids but this was of recent origin. Microscopic examination revealed the typical thin-walled venous lakes with some areas of the lesion showing chronic inflammatory cells and evidence of fibrosis. No area of malignant change was noted in any microscopic section.

The sigmoid colostomy was closed uneventfully on April 11, 1960, 5 months after the removal of the tumor. At this writing, the child is 13 months of age and is having normal bowel movements by rectum. Anal sphincter function is difficult to evaluate, however, and possible incontinence may require a corrective operation in the future. The cosmetic result is very satisfactory (Fig. 3).

DISCUSSION

There is great variance of opinion concerning therapy for hemangiomas, particularly for those seen in infants. The pathologic type, growth pattern, location, and size all play a significant role in determining the form of treatment to be employed. Since spontaneous involution of certain hemangiomas is well documented, it is only natural that most clinicians favor a conservative attitude for many patients with these vascular tumors. Careful observation of the growth pattern of these lesions, as stressed by Lampe and Latourette,[9] may be most significant. These authors have emphasized that lesions which show rapid enlargement in the first 6 to 8 months of life are most prone to spontaneous involution. This process often starts when the child is approximately 1 year of age and is usually complete by the time the child is 5 years old. Conversely, hemangiomas noted at birth which show a very slow growth pattern rarely undergo spontaneous regression. The case reported above presented such a pattern. This phenomenon of disappearance, without any therapy, is a common occurrence with the hemangioma simplex (strawberry mark) but is seen less often with the cavernous type of lesion and rarely with the capillary hemangioma (port wine mark). There is much controversy concerning the regression tendency of the cavernous type of lesion. Duncan,[8] in his original careful observations on vascular tumors, advocated the conservative approach although he did emphasize that the complications of ulceration and bleeding often necessitated surgical intervention. Lister,[10] in 1938, re-emphasized the value of the expectant attitude and stated that the majority of hemangiomas could be left alone. He stressed the fact that even the cavernous type often disappeared without active treatment. Other members of this conservative school include Ronchese,[12] Brain and Colnan,[4] Sulzberger and Wolf,[13] Watson and McCarthy,[14] and Becker and Obermayer.[2] On the other hand, Andrews and associates,[1] reporting on an extensive experience, stated that only 11 per cent of 135 cavernous hemangiomas underwent spontaneous involution and this often was aided or initiated by x-ray therapy. The attitude against expectant treatment has been emphasized by Blackfield and colleagues,[3] Davis,[7] Phalen,[11] and Costello,[6] all of whom believe that only a small percentage of true cavernous lesions should be left untreated. Brown and Fryer[5] have documented the improvement in cosmetic results when plastic surgery is employed early for these growths. They pointed out that, on occasion, considerable cosmetic deformity can occur with large hemangiomas which are treated conservatively over a long period of time.

Although a conservative approach had originally been adopted in our case, the in-

effectiveness of the roentgen therapy and attempts to produce sclerosis soon became obvious. Serious bleeding, ulceration, and infection of the vascular mass left little choice for treatment short of complete surgical removal. As anticipated, there was extensive blood loss during the staged procedures and accurate blood replacement was of prime importance. The location of the tumor with involvement of the anus and a portion of sphincter musculature presented an additional problem. Accurate appraisal of the degree of impairment of anal continence is not possible at this writing.

It was apparent during the actual operation that, although the bulk of the tumor was confined to the subcutaneous tissue, the enormous venous channels feeding the hemangioma via the perineal layers had been unaffected by the sclerosing material. Furthermore, it was difficult to speculate that such large vessels could be reduced in size by radiation therapy or that they would regress without some form of active treatment.

The cosmetic result was surprisingly good in this case despite the very extensive denuded surface which remained after removal of the growth. At present, there appears to be only minimal distortion of the vaginal orifice and no cicatricial stenosis of the anal opening has been noted to date.

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Recent Advances in Surgery

Conducted by ALFRED BLALOCK, M.D.

Eventration of the diaphragm

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Eventration of the diaphragm is the abnormal elevation of one phrenic leaf as a result of aplasia, paralysis, or atrophy. The condition has been regarded as rare, infrequently productive of symptoms, and requiring no treatment.[15] The very name has been considered a gross misnomer and the etiology thought to be obscure. This paper will describe diaphragmatic eventration as a not infrequent acquired condition, producing symptoms at times serious or discomforting, and for which surgical correction is both functionally and symptomatically satisfactory. Four representative cases illustrating the infantile and adult types of eventration will be discussed.

Petit gave the first clear postmortem description of eventration in his posthumously published book on surgery and Beclard is credited with having coined the term. "Eventration," which means "out of (e) the belly (venter)," suggests herniation of peritoneal contents through the abdominal wall. The addition of the word "diaphragm," however, clarifies the direction of the intra-abdominal extrusion. Other suggested terms, including "relaxatio diaphragmatica," "idiopathic high-lying diaphragm," "idiopathic eventration," "relaxed diaphragm," "insufficiency of diaphragm," "high level of diaphragm," and "elevation of diaphragm," are no more descriptive than "eventration" and have never been accepted into common usage.

The diagnosis of eventration was difficult prior to the use of roentgenograms, and Bergman, in 1913, was able to collect only 32 cases in the world literature. Korns,[32] in a scholarly paper, assembled 65 cases in 1921 and Reed and Borden[45] reviewed 183 cases in 1935. The first suggestion that surgical plication of the diaphragm was warranted if symptoms were sufficiently disabling or distressing was made by Wood[55] in 1916. Seven years later Morrison[40] accomplished the first successful repair in a 10-year-old girl with immediate relief of symptoms. There were only 11 cases of eventration in infants reported prior to the first successful repair in a 6-week-old male by Bisgard[6] in 1947. Partial eventration as a surgical condition was described by Nylander and Elfving[43] in 1951.

The fact that in 1954 only 300 cases had been reported[1] attests to the rarity of eventration of the diaphragm. In chest roentgenogram surveys elevation of the diaphragm is seen in the ratio of 1 to 1,400 films. Beck and Motsay[3] found 4 per cent of 2,500 newborn children to have diaphragmatic elevation by x-ray examination, but stated that only 3 had severe respiratory difficulty. Kinzer and Cook[30] examined roentgenograms of 412,149 inductees and found asymptomatic idiopathic eventration in 31. In Denmark, 38 eventrations were found in 107,778 x-ray examinations.[14] Although these surveys may reflect the frequency in the general population, Wynn-Williams[57] frequently found acquired eventration in chest clinic patients and considered it a comparatively common palsy.

Eventration may be congenital or acquired in origin and both types may be total or partial in extent. In the congenital elevation, weakness is not truly total since the anterior portion, derived from the septum transversum, does not have the same anlage as the posterolateral portion and does not take part in the eventration. The large congenital eventration is the result of incomplete or absent muscularization of the pleuroperitoneal membrane[19] and the partial eventration involves a segment of this membrane. These congenitally weak areas may be pierced by systemic vessels entering the inferior pulmonary ligament or lung and there may be associated extralobar sequestration of the lung.[4, 16, 52] Congenital eventration is seen in the fetus and may be associated with other anomalies, including aplasia of the lung, high renal ectopia, hypoplastic aorta, ptotic eyelids, cleft palate, torticollis, transposition of the abdominal organs, faulty rotation of the colon, undescended testicle, and club feet. The congenital elevation suggests a malformation which is similar to the congenital Bochdalek hernia in that both occur more frequently in the male (2 to 1) and most often on the left (8 to 1),[45] and the thick anterior muscular septum is always present.[31] When there is weakness or absence of posteromedial muscular ridge of the diaphragm, eventration or hernia is accompanied by high renal ectopia.[9] Microscopic examination of the area of eventration, when recorded, shows deficient or degenerated muscle fibers. The phrenic nerve is found to be normal or slightly diminished in size with no microscopic evidence of degeneration or inflammation.

Acquired eventration may be due to phrenic nerve or muscle involvement. At birth, breech presentation and difficult delivery may produce phrenic nerve injury with or without brachial paralysis.[1, 7, 8, 19, 26] Irritation of the phrenic nerve along its course by tumor, suppuration, or fibrosis may result in temporary or permanent injury.

Phrenic nerve lesions due to poliomyelitis, herpes zoster, dystrophia myotonica,[12] diphtheria, influenza, syphilis, antitetanus serum, alcohol, and lead poisoning have been reported.[57] Cervical caries, pericarditis, subphrenic abscess,[29] aneurysms, and echinococcus infection of the liver[37] have also been associated with diaphragmatic paralysis.

Phrenic nerve crush in the treatment of pulmonary tuberculosis in the past has led to an extensive clinical study of diaphragmatic paralysis. After crushing of the phrenic nerve in the neck, there is usually a 6-month period of total paralysis of the diaphragm with gradual restoration of function. In the absence of an accessory phrenic nerve the diaphragm gradually regains its mobility, may remain paralyzed, or there may be residual or segmental paralysis. Occasionally the paralyzed diaphragm is elevated only after the initiation of pneumoperitoneum.[57]

Paralytic elevation of the diaphragm has been reported after thoracic and abdominal infection and operations.[19, 27, 37] In the first few weeks after an uncomplicated abdominal operation the diaphragm may be elevated, its movement diminished, and the lower lung segments compressed. Freedman[24] described the development of phrenic paralysis during or after pneumonia or lung abscess. In 2 patients the paralysis developed at the onset of illness, in 4 the diaphragm became paralyzed after approximately 5½ weeks, and in 2 it remained permanently immobile. Couch,[18] in 1953, reported 16 cases of eventration seen in a 2-year period. Five followed recent pneumonia and 4 of the patients recovered in 2 to 12 months with 1 having dissociated paralysis of the anteromedial segment. In no case was pleurisy or tumor evident. In 4 years, Wynn-Williams[57] collected 10 cases of paralysis without elevation of the diaphragm. In 7 of the patients the condition remained unchanged, but there was partial return of function in 3. He noted that the paralyzed right side of the diaphragm is less apt to become elevated. During the same 4-year period he found 5 paralyzed diaphragms, 2 on the right and 3 on the left, with 3 re-

maining unchanged for 1 to 4 years. Meylar[37] collected 12 cases of temporary eventration in a few years and noted all but one was on the right. Eventration followed cholecystitis in 1, 6 developed after cholecystectomy, and 5 accompanied lung disease. Normal motility returned within a few weeks in all cases. MacLeod[34] found that eventration developed in 50 per cent of patients with pulmonary infarcts and 8 per cent remained permanently disabled. Christensen[14] reported a case of permanent eventration after pneumonia. In another instance, temporary elevation was noted during pneumonia with gradual improvement in 8 months and normal motion in 3 years. He found 3 patients with permanent phrenic paralysis who retrospectively gave a history of pneumonia.

Acquired *partial* eventration may be due to local muscular weakness from contiguous inflammation, segmental nerve damage, or incomplete recovery after complete nerve paralysis.[43] The last type of dissociated paralysis is probably the most common and occurs more frequently on the right side.[22] As the diameter of the local weakness diminishes, its resemblance to diaphragmatic hernia increases, with increasing likelihood of incarceration of bowel on the left and liver on the right.[44, 54]

PATHOPHYSIOLOGY

The motion of the elevated diaphragm may be normal, diminished, absent, or paradoxical. With the abnormal elevation there is some degree of lung compression and shifting of the mediastinum with respiratory effort. In the paralyzed diaphragm the serious physiologic disturbance is due to shifting of the mediastinum to the normal side on inspiration. When the right side of the diaphragm is paralyzed there is slight rotation of the heart to the left, but with left paresis rotation is marked and there is tracheal as well as aortic arch rotation.[21] The lack of central tendon fixation because of weakened crural fibers allows for greater compression of the medial side of the mediastinum by intra-abdominal pressure.[23] With diaphragmatic paralysis the uninhibited intercostal muscle produces divergence of the costal margin on that side with an increase in the transverse as well as anteroposterior diameter of the lower chest wall. This sign, first described by Hoover[29] in 1913, depends upon the imbalance of the intercostal muscles pulling the costal margin outward and the diaphragm pulling the margin and sternum inward. The sign is best noted by placing the thumbs over the costal margin and noting the angle of motion from xyphoid to the posterior axillary line.

Sarnoff[47, 48] demonstrated in animals and man that stimulation of one phrenic nerve results in ipsolateral diaphragmatic motion with the opposite side of the diaphragm remaining motionless except for slight inspiratory upward movement and minimal mediastinal shift toward the stimulated side. He found that spontaneous respirations ceased with electrophrenic stimulation and the lung on the unstimulated side was ventilated almost as much as the lung on the ipsolateral side. The contralateral lung exhibited normal oxygen uptake and there were normal arterial oxygen and carbon dioxide gas tensions. With an increased rate of nerve stimulation the ventilation of the unstimulated side is slightly diminished, but never more than 16 per cent of normal. Christensen[14] recently reported 3 cases of eventration in which the patients were treated by surgical plication with restoration of the diaphragm to its normal position. After operation, the diaphragm remained paralyzed with slight paradoxical motion, but bronchospirometry showed almost normal lung ventilation and oxygen uptake on the affected side.

With elevation of the left side of the diaphragm the fundus of the stomach may be elevated or rotated so that the greater curvature lies beneath the diaphragm. The stomach may not only be inverted but volvulus, partial or complete, may be present with some obstruction to passage at either the cardia or pylorus.[31] In right phrenic paralysis the pyloric end of the stomach moves toward the right; the gall bladder is elevated and may not empty completely after a fatty meal.

DIAGNOSIS

Clinically, eventration can best be classified as infantile or adult in type. In the infant serious respiratory difficulty may develop in both congenital and acquired elevations with rapid, irregular respiratory movements and cyanosis. Acquired paralysis may follow breech or difficult delivery, with or without Erb's palsy, and the symptoms may be immediate or delayed. In some so-called congenital elevations, when respiratory difficulty develops after the second or third day, it is possible that aspiration or pneumonia may be responsible. The respiratory distress occasioned by eventration can be differentiated from intracranial hemorrhage, lobar emphysema, atelectasis, diaphragmatic hernia, pneumonia, and congenital heart disease by chest fluoroscopy and roentgenograms. The severe symptoms in the infant are due to the shift of the labile mediastinum with inadequate ventilation of the opposite lung and torsion of the heart and great vessel. If symptoms fail to appear within the first 5 years of life it is said the patient will usually be without symptoms until the fourth or fifth decade, when decreased cardiopulmonary reserve together with increased intra-abdominal pressure due to obesity, obstipation, or tumor may precipitate digestive or respiratory symptoms.[14, 45]

The most common symptoms in the adult, especially with the left eventration, are dysphagia, epigastric pain, heartburn, and belching. The abdominal pain is sometimes relieved by lying on the right[13] or left side,[14] depending upon the degree and type of inversion or volvulus. From his experience in therapeutic phrenic crush, Harper[28] found 2 distinct syndromes. In left phrenic paralysis there was often decreased appetite, fullness, nausea, and vomiting, and with right paralysis there was apt to be right upper quadrant pain simulating gall-bladder disease with anorexia, distention, and nausea. In 159 temporary nerve paralyses, he found that symptoms disappeared after diaphragmatic activity returned but in 14 patients with permanent paralysis, 2 developed peptic ulcerations and 1 suffered melena. Symptoms occurred in 25 per cent of all patients with therapeutic nerve paralysis and developed immediately or within 12 weeks after operation. Christensen[14] followed 5 patients with asymptomatic eventration for 3 to 12 years. Three of the 5 subsequently and suddenly developed symptoms and in 1 there was a concomitant marked increase in body weight. In 1 patient, incomplete repair of the diaphragm corrected the inverted stomach but did not reduce the leaf to its normal level. The operation resulted in relief of digestive symptoms but there was continued respiratory difficulty.

Eventration of the diaphragm of the infant produces marked symptoms of respiratory distress with cyanosis noted especially after feeding. The respirations are apt to be crowing and irregular. Careful examination of the child in the supine position will reveal a see-saw cyclic motion which begins with inspiratory epigastric bulging on the normal side followed by rising of the epigastrium on the opposite side, progressive expansion of the anterior chest wall above, and finally shifting of the expansile motion to the normal anterior chest wall. Tyson and Bowman[51] first noted the lack of epigastric bulging on inspiration in congenital eventration. Hoover's sign is always present when the diaphragm is sufficiently elevated or paralyzed. Percussion note over the affected side may be flat or tympanitic, depending upon the underlying displaced organs, and occasionally bowel sounds may be heard. Routine posteroanterior chest roentgenograms will usually show the elevated diaphragm, although at times it is necessary to take lateral and oblique films in order to visualize the entire intact leaf. On fluoroscopic examination the degree of diaphragmatic motion may be noted, as well as the presence of mediastinal shift, intercostal muscle action, abnormal ventilation, and parenchymal lung changes. A sudden, forceful inspiration, or "sniff test," will provoke the paradoxical motion seen fluoroscopically in cases of paralytic eventration. A markedly elevated, nonparalyzed congenital lesion will produce similar motion, but Chin[13] main-

tains that this is not truly paradoxical, but merely passive upward motion which occurs until the slack is taken up and descent of the diaphragm begins. The unelevated paralyzed diaphragm can be easily identified by fluoroscopy. The use of pneumoperitoneum is invaluable in raising the nonelevated paralyzed diaphragm, as well as in delineating total and partial eventrations, diaphragmatic hernias, and tumors of the diaphragm. When pleural thickening or adhesions are present it may be impossible to differentiate between eventration and diaphragmatic hernia. Supradiaphragmatic fluid loculations may simulate a high diaphragm but appropriate decubitus roentgenograms should expose its normal position.[53] The use of phrenic nerve stimulation to determine the presence or absence of paralysis is of no clinical value since the test itself is difficult to perform and treatment depends in the main upon symptoms. Bronchoscopy and bronchograms are unnecessary and even dangerous to the infant, but the possibility of secondary phrenic paralysis due to tumors or pulmonary infection in the adult may make these tests worth while. In spite of adequate ancillary examination, surgical exploration alone may be necessary to determine the nature of the lesion.

TREATMENT

Restoration of the diaphragm to its normal position helps stabilize the mediastinum, prevents rotation of the heart, and allows almost normal ventilation and oxygen uptake of the lung. Correction of the left leaf will also restore the stomach and splenic colon to their normal positions. In infants, surgical correction of the symptomatic elevated diaphragm is mandatory. It is unnecessary to differentiate between the congenital and acquired symptomatic lesions, since they are both cured by operation. Gans[25] and others have stated that they have seen "an infant die when an operation was delayed." Christensen[14] believes that paralysis without elevation in the infant may be treated expectantly by positioning the child on the affected side in order to stabilize the mediastinum, using oxygen if necessary, and operating only if symptoms worsen. In the adult, operation is usually indicated when symptoms are severe. Surgical repair, however, should be considered in the person with an asymptomatic high diaphragm before degenerative cardiopulmonary changes develop, with the knowledge that ventilation and respiration will improve.

The repair of eventration of the diaphragm consists of excising or shortening the area of weakness and thereby restoring it to a position of midexpiration. Since the paralysis in the infant may be temporary, care should be taken not to disturb the nerve by injection, crushing, or snaring in a suture. The transthoracic route through the posterolateral seventh or eighth intercostal space gives the best exposure of the diaphragm and allows complete exploration of intrathoracic organs. State and others[50] have used the abdominal approach in the infant, but although the exposure is limited, it allows inspection of other congenital anomalies such as malrotation of the bowel. The inelastic or redundant tissue may be retracted with forceps, overlapped, plicated, or inverted with a series of purse-string sutures. Some surgeons have resected the weakened areas but branches of the phrenic nerve may inadvertently be damaged.[35] When there is absence of the posteromedial muscle, as occurs with high renal ectopia, a patch of Teflon cloth (or Marlex) may be used to reinforce the area of weakness. Sanford[46] and Monahan[39] have used tantalum mesh, but this material fragments and may be dangerous. The right phrenic nerve supplies both right and left esophageal crura and should be carefully preserved during resection or suture.[17]

RESULTS

In congenital or acquired eventration in infants, the results after surgical repair have been unequivocally good. While it is true that the infant with temporary elevation of the diaphragm may be relieved by supportive measures alone, the risk of delay is

greater than the risk of operation. Children beyond the first month of life who have repeated respiratory infections due to inadequate ventilation and cough may be relieved by restoration of the diaphragm to the normal position. Serious respiratory symptoms have been cured by replacement of the diaphragm in its midexpiratory position despite continued muscle paralysis.[7] In the adult, respiratory symptoms not due to primary pulmonary or cardiac disease are improved by surgical correction. When digestive symptoms are associated with rotation of the stomach, repair of the left eventration has been followed by excellent results. In the symptomatic partial eventration, operative repair has been of value when there is incarceration of bowel or liver and when aberrant systemic vessels with or without extralobar sequestration are present.

CASE REPORTS

Case 1. L. H., a 2-week-old boy, was admitted March 8, 1957, because of increasing respiratory difficulty and cyanosis. He had been born with club feet, hypospadius, and bilateral entropion, and had had rapid, labored breathing since birth. At the time of birth his respiratory distress had been associated with an umbilical cord wrapped tightly about his neck. Oxygen was administered for 12 to 15 hours with improvement, but there was marked respiratory distress when he was fed. On admission the respirations were labored and had a peculiar crowing character. Cyanosis was present when the infant cried or was fed. The right side of the chest was dull to percussion with decreased breath sounds throughout. Examination of the chest and abdomen showed see-saw cyclic respiratory motion. In sequence, inspiratory elevation of the left side of the epigastrium was followed by right epigastric bulging, then elevation of the right anterior side of the chest, and finally of the left anterior side of the chest. A high right leaf of the diaphragm was seen on roentgenogram and fluoroscopy showed paradoxical motion with compression atelectasis of the right middle and lower lobes (Fig. 1). Because of continued severe respiratory distress operation was performed that night through an anterolateral fifth intercostal space incision. Pleural adhesions were found binding the right upper and middle lobes to the chest wall and the pericardium to the diaphragm. The right lung was small and partially atelectatic, but expanded well with positive pressure anesthesia. The diaphragm was thin, atrophic, and immobile, and biopsy showed only membranous tissue. The diaphragm was restored to its normal position by imbrication with 2 layers of silk sutures. The postoperative course was entirely uneventful and there was no further respiratory difficulty (Fig. 2). The patient went home and was apparently in good health until 1 month later when he aspirated vomitus after eating and died of asphyxia en route to the hospital.

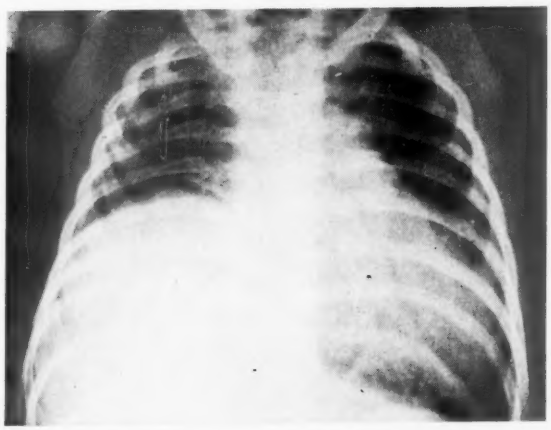

Fig. 1. Case 1. Elevated, paralyzed right diaphragm in 2-week-old boy with severe respiratory distress.

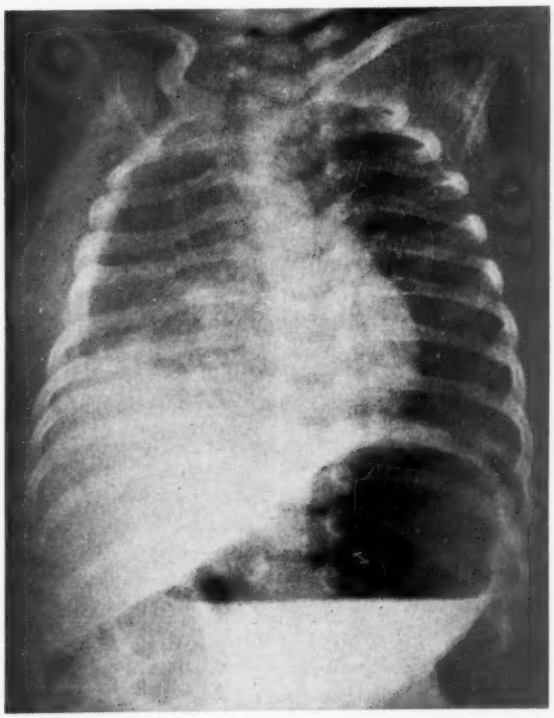

Fig. 2. Case 1. Diaphragm in normal position after repair. It is immobile and there are no respiratory symptoms.

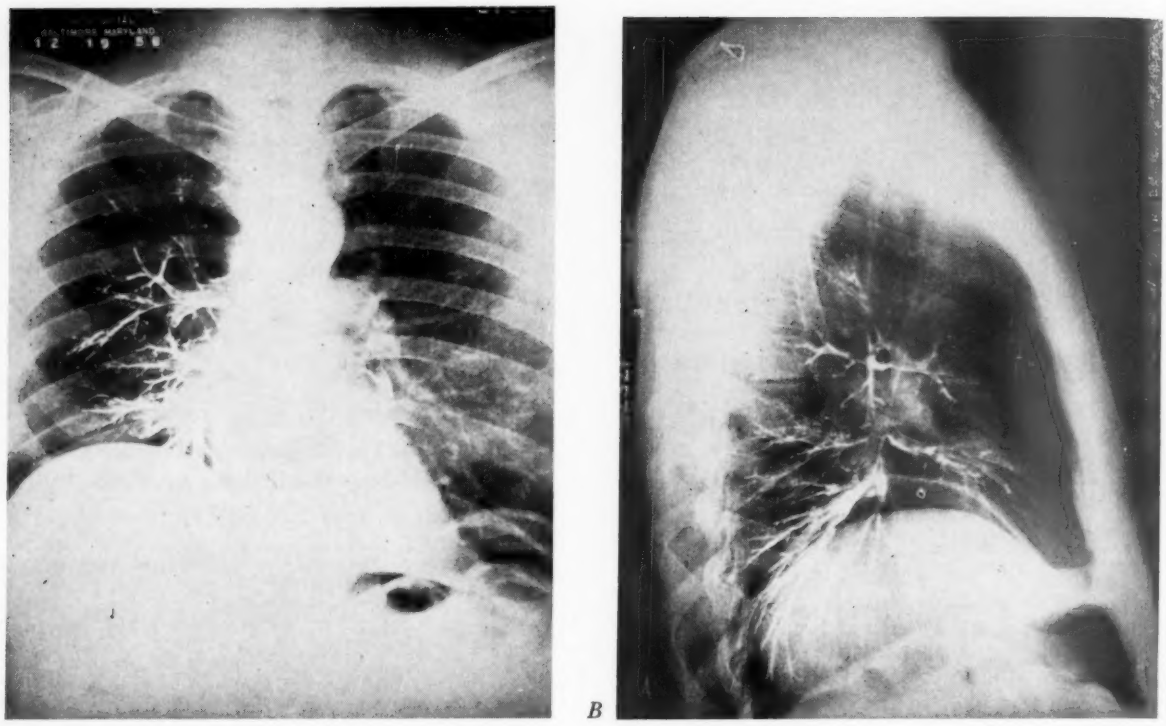

Fig. 3. Case 2. *A,* Adult total eventration acquired after "severe cold" 6 months before admission. There are mild respiratory symptoms. *B,* Bronchogram with pneumoperitoneum showing extension and right lower lobe compression.

The typical congenital eventration is an elevation without paralysis of the posterolateral portion of the left side of the diaphragm. This infant had numerous congenital anomalies but the right side of the diaphragm was paralyzed and there were pleural adhesions binding the lung to the chest wall. In Shellito's[49] case No. 4 the patient also had adhesions binding the diaphragm to the pericardium, mediastinum, and pleura. It is possible that intrauterine pneumonia had been responsible for the phrenic paralysis. Operation produced remarkable relief of all respiratory symptoms but unfortunately the child died later of unrelated causes.

Case 2. W. L. B., a 49-year-old man, had developed pain in the right side of the chest, cough, and dyspnea after a "severe cold" 6 months before admission on Jan. 5, 1959. On admission he complained of cough, fatigue, and was dyspneic on walking up 1 flight of stairs. He had no digestive symptoms. Physical examination showed no remarkable signs. The lungs were clear to percussion and auscultation. Chest roentgenograms and fluoroscopy showed partial atelectasis of the right lower lobe and an elevated right side of the diaphragm exhibiting paradoxical motion. Pneumoperitoneum disclosed an intact, elevated right phrenic leaf with compression of the lower lobe (Fig. 3). Bronchoscopic and bronchographic examinations were not remarkable. A right posterolateral thoracotomy through the eighth intercostal space showed the diaphragm to be markedly elevated with a greater part of the leaf thinned and almost translucent. The lung and phrenic nerve appeared normal. After plication a small degree of motion was noted without paradox. Postoperative roentgenograms showed the left side of the diaphragm to be elevated with posterior segmental atelectasis of the left lower lobe. This condition was relieved by bronchoscopic aspiration on the fifth day and the left side of the diaphragm gradually returned to its normal position (Fig. 4). Prior to discharge on Jan. 20, 1959, the left side of the diaphragm moved well and the right leaf was in normal position with slight motion. Biopsy of the diaphragm showed scarred striated muscle.

This case represents an acquired total eventration of the diaphragm. The onset of symptoms 6 months before admission associated with cough and chest pain would suggest that this patient had a pulmonary infection with associated diaphragmatic paralysis. Development of postoperative atelectasis with elevation and temporary paralysis of the left side of the diaphragm may have resulted from torsion of the contralateral diaphragmatic leaf at operation. One year later the patient no longer complained of dyspnea or

cough and had no sense of fatigue or disability.

Case 3. J. M., a 41-year-old man, was admitted on April 15, 1958, because of dyspnea and heartburn. In November, 1957, he had fallen from a ladder and during descent had been struck in the epigastrium by a jutting wooden joist. He suffered immediate shortness of breath and shortly thereafter noted subcostal pain, substernal burning, and a sour taste in his mouth when lying on his right side. Roentgenograms of the chest showed the left side of the diaphragm to be high and immobile with partial atelectasis of the left lower lobe. After a barium swallow, straightening of esophagocardiac angle with esophageal reflux and a partial volvulus of the stomach was seen (Fig. 5). Chest roentgenograms taken 4 years before had shown no abnormality of the diaphragm. Moderate esophagitis was seen endoscopically. At operation the left side of the diaphragm was seen to be elevated and paralyzed. There was an area of granulation 2 cm. in diameter noted on the pleural surface of the diaphragm just distal to the insertion of the left phrenic nerve. The superior half of the diaphragm was atrophied and the inferior portion much thinner than normal. A large sliding esophageal hernia was present but the crura appeared normal. Repair of the hiatus hernia was accomplished by incising and suturing the proximal edge of the phrenicoesophageal ligament to the peritoneal surface of the diaphragm and reducing the hiatal opening with posteriorly placed crural sutures. The fundus of the stomach was then sutured to the anteromedial portion of the diaphragm in order to increase the cardioesophageal angle. The diaphragm was restored to its normal position by imbrication. The postoperative course was complicated by partial atelectasis of the right lower lobe and elevation of the right side of the diaphragm. A roentgenogram taken before discharge showed both sides of the diaphragm in normal position (Fig. 6) with no motion of the left leaf and no mediastinal shift. A small hiatus hernia and slight esophageal reflux is still evident.

This is an unusual case of indirect injury of the left phrenic nerve at its insertion into the diaphragm with segmental paralytic eventration. Whether or not this injury contributed to the development of the esophageal hernia is not known but it is noted that the digestive symptoms developed coincidentally with the accident and the correction of the gastric volvulus was followed by diminished discomfort in spite of continued reflux. Reed and Borden[45] cite 3 cases of eventration after injury and DiPierron[45] reported the sequence of a man who fell down, immediately became dyspneic, and later was found to have a left eventration. Wood and Wood[56] noted an instance of temporary left eventration after an automobile accident and Wynn-Williams[57] re-

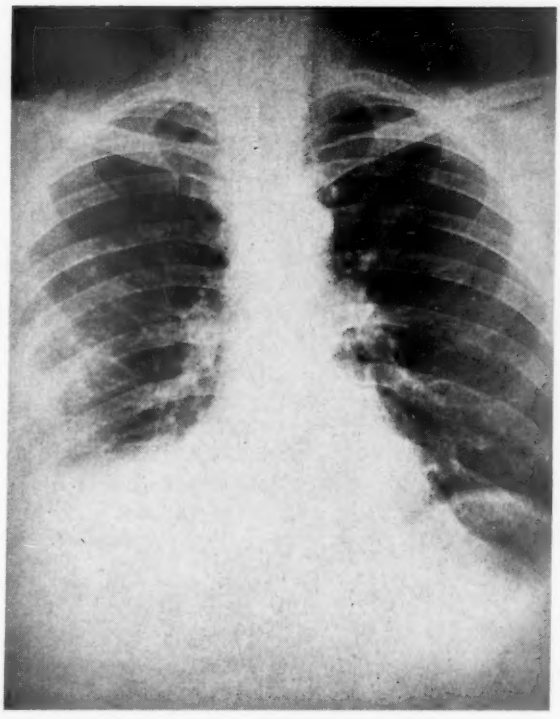

Fig. 4. Case 2. Paralyzed diaphragm restored to normal position. There are no symptoms.

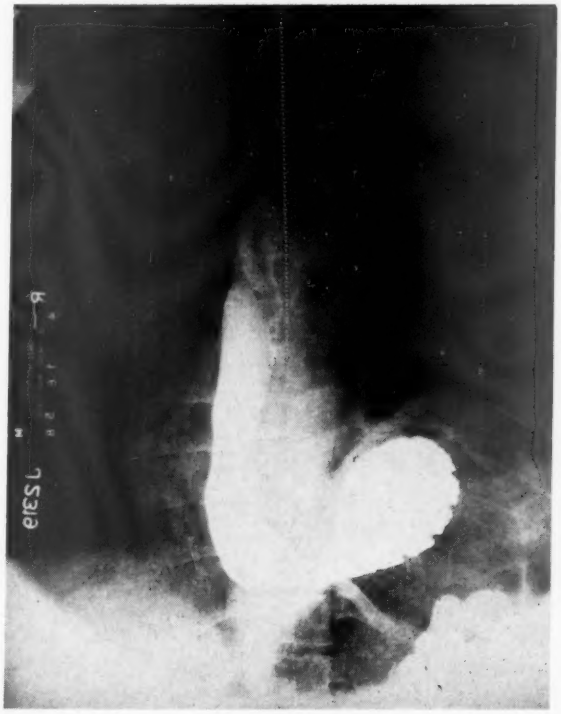

Fig. 5. Case 3. Adult eventration acquired by indirect trauma to epigastrium with gastric volvulus and esophageal reflux. There are severe respiratory and digestive symptoms.

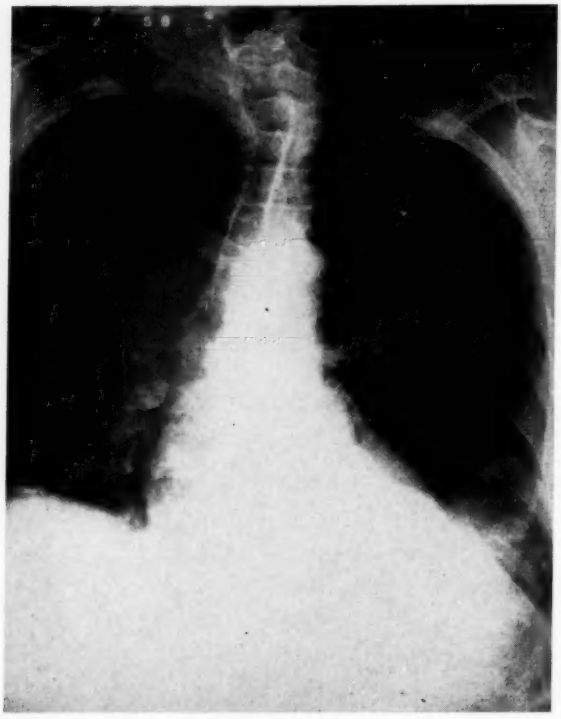

Fig. 6. Case 3. Paralyzed diaphragm restored to normal position. There is no respiratory distress, only mild digestive symptoms due to esophageal reflux.

Fig. 7. Case 4. Partial asymptomatic congenital eventration in adult.

ports the case of a patient with injury to the left side of the chest who developed persistent exertional dyspnea and was found to have an eventration 5 years later. Respiratory symptoms associated with eventration and mediastinal shift were completely relieved by restoration of the diaphragm to its normal position. The attempted restoration of the cardioesophageal angle by suturing the gastric fundus to the atrophic diaphragm was unsuccessful. Nissen's[42] use of fundic plication might have produced better results.

Case 4. J. Y., a 43-year-old white man, was admitted on Oct. 17, 1957, because of cough and pain in the right side of the chest of 1 month's duration. In 1938 he had been hospitalized for 2 months for a lung condition and at that time was told that he had a shadow in his right lung. He had been in excellent health until 2 weeks prior to admission. Physical examination was not remarkable. Roentgenograms showed a mass in the region of the right cardiophrenic angle (Fig. 7) which appeared to be attached to the dome of the diaphragm. Tomography (Fig. 8) indicated a discrete mass above the diaphragm which was thought to be a tumor. At operation, through a right posterolateral eighth intercostal space approach, partial eventration of the posterior segment of the diaphragm lateral to the inferior vena cava was found. Through this 6 cm. weak area, liver bulged upward for a distance of 6 cm. A small vessel traversed the sac and entered the right lower lobe by way of the inferior pulmonary ligament. A biopsy of the sac showed no muscular tissue. During the postoperative period elevation of the opposite side of the diaphragm with partial atelectasis of the left lower lobe developed. This temporary eventration cleared in a short time and prior to discharge there was normal and active motion of both sides of the diaphragm (Fig. 9).

This patient with partial eventration of the right side of the diaphragm with minimal symptoms was operated upon when tumor was suggested by tomography. Pneumonia in 1938 may have produced a temporary diaphragmatic paralysis with subsequent dissociate paralysis and localized eventration, but the presence of a small vessel leading to the right lower lobe traversing this space and the absence of muscle fibers in the sac wall suggests congenital origin. The follow-up examination 2 years later showed no return of symptoms or eventration.

DISCUSSION

Eventration of the diaphragm, from the clinical standpoint, is best classified as infantile or adult in type. Chin[18] would restrict the term to congenital nonparalytic eventration, but since the symptoms, signs, treatment, and results are identical for both congenital and acquired elevations, this limited definition would serve no valid purpose. Case 1 introduces the possibility that intrauterine pneumonia can be responsible for the eventration and makes the differentiation between congenital and acquired dis-

ease even more difficult. The great majority of adult eventrations are due to disease. There are sufficient clinical observations in addition to those in Case 2 to support the fact that pneumonia, lung abscess, pulmonary infarcts, cholecystitis, cholecystectomy, and subphrenic abscesses may produce temporary or permanent diaphragmatic paralysis. Partial eventration may be congenital as in Case 4, but also may be the result of dissociated or residual segmental paresis of the diaphragm (Case 3). The most valuable clinical sign of eventration is the uninhibited divergence of the costal margin from the midline on inspiration (Hoover's sign). The see-saw respiratory motion of the epigastrium and anterior chest wall is a significant diagnostic sign in the infant. Fluoroscopy remains the basic diagnostic tool. It will show the extent of the eventration, the degree of paradoxical motion and mediastinal shift, the unequal costal margin motion, and the presence of thoracic disease and will detect gross pulmonary function impairment.

All surgeons would agree that patients with infantile symptomatic eventration should be operated upon without delay. No objection should be made to the operative correction of adult eventration when respiratory symptoms are present. The adequate ventilation and respiration with unilateral phrenic stimulation in Sarnoff's experiments[47, 48] suggests that even the asymptomatic high elevation would be benefited by restoration of the diaphragm to its normal position. The occasional patient with digestive difficulties attributed to rotation of the stomach will also be helped by restoration of the diaphragm to its proper level. Partial eventration has been considered to be a type of diaphragmatic hernia[36] and should be repaired if symptomatic. In addition, operation may be necessary when the possibility of tumor or diaphragmatic hernia cannot be excluded. Supradiaphragmatic cyst formation with eventration may be accompanied by an aberrant systemic vessel piercing the elevated diaphragm and should be searched for at the time of operation.[4, 16, 48]

Fig. 8. Case 4. Tomogram which shows irregular mass above right side of diaphragm at cardiophrenic angle.

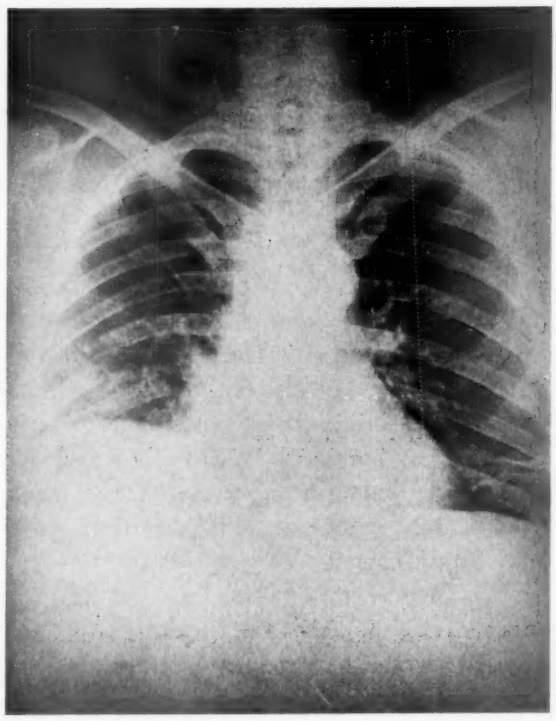

Fig. 9. Case 4. Partial eventration repaired after reduction of herniation of liver and resection of anomalous transphrenic systemic artery.

Few surgical failures in the maintenance of the restored normal position have been reported.[41] When inadequate elastic tissue is available for closure or imbrication, additional material may be obtained by freeing the diaphragm from the pericardium[38] or by using a nonirritating prosthetic fabric such as nylon or Marlex. No complications have been reported in any surgical series but 3 of the 4 patients in the cases presented here developed temporary elevation of the opposite side of the diaphragm with partial basal atelectasis postoperatively. This high incidence of eventration may suggest either increased susceptibility of the patient or a normal reaction of the contralateral side of the diaphragm to transverse pull or torsion. The latter possibility is now being investigated.

SUMMARY

1. Eventration of the diaphragm is best classified clinically as infantile or adult in type. The infantile eventration may be congenital or acquired, is usually accompanied by serious respiratory distress, and should be treated surgically. Operation is curative and risk is minimal.

The adult type of eventration is usually an acquired disease secondary to pneumonia, pulmonary infarcts, thoracic and abdominal operations, and cholecystitis. The diaphragm may remain temporarily or permanently paralyzed, or may incompletely recover with dissociated or partial paralysis. Symptoms may be either respiratory or digestive. Surgical correction is indicated when symptoms persist and are well defined.

2. The diagnosis of eventration may be made by the presence of Hoover's sign and chest roentgenograms, although at times pneumoperitoneum as well as barium series may be necessary.

3. High elevation of the diaphragm markedly diminishes the ventilation and oxygen uptake of the lung on that side and mediastinal shift impairs the function of the contralateral lung. Surgical restoration of the paralyzed diaphragm to its normal position will prevent mediastinal shift and produce almost normal ventilation and oxygen uptake. In the young, vigorous adult with an asymptomatic elevated diaphragm operative correction of the diaphragm is of great functional value.

4. Partial eventration may be congenital and associated with extralobar sequestration and/or perforating systemic vessels. Both congenital and acquired partial eventrations, like the small hernia sac, may incarcerate the bowel or liver and, if symptomatic, should be repaired.

5. Eventration of the diaphragm is neither rare nor asymptomatic and treatment is indicated in specific asymptomatic as well as symptomatic patients.

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Historical development of the surgical mask

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Hoold cloos thy mouth, man, by thy fader kyn. . . .
Thy cursed breeth infecte wole us alle.
Geoffrey Chaucer

In the classical illustrations of great surgical events prior to 1900, such as those of Ephraim McDowell's ovariotomy (Fig. 1) or Morton's administration of a general anesthetic (Fig. 2), the participants and observers are depicted in street clothes. Apparently the surgeons and their assistants made little effort to alter their everyday clothes during the performance of operative procedures. Surgical caps, gowns, gloves, and masks were not customarily used.

What are the origins of the typical modern operating-room apparel (Fig. 3), particularly the surgical mask?

Pasteur demonstrated that bacteria are the agents responsible for infection. The use of chemical antisepsis, introduced by Lister in 1867, was the first attempt to combat the adverse action of these microorganisms in wounds. By the end of the nineteenth century, most surgeons had accepted Lister's concept that bacterial contamination predisposed postoperative infections.

In 1883, Gustav Neuber introduced the wearing of a sterilized surgical gown and cap.[14] At Johns Hopkins Hospital, under the direction of William Halsted, the importance of aseptic surgical technique was further emphasized by the introduction of rubber gloves (Fig. 4). These gloves were first used by an operating-room nurse in the winter of 1889.[8] They were utilized by all operating-room personnel in 1896 at the suggestion of F.G.C. Bloodgood, then Assistant Surgeon at Johns Hopkins.[7]

Interestingly enough, it was only after caps, gowns, and gloves had already been generally accepted that the use of a surgical mask was first reported.

In 1897, Johann von Mikulicz-Radecki[11] of Breslau, Germany (Fig. 5), described the use of a surgical mask consisting of a single layer of gauze, the so-called Mundbinde, which had the advantage of covering not only the nose and mouth, but also the beard. The main purpose of his paper, however, was to advocate the routine use of cotton gloves during surgical operations. The mask was mentioned only in passing.

In the same year, Prof. Fluegge,[5] a colleague of Mikulicz in Breslau, documented the importance of air-borne bacteria in wound infection. In a detailed experimental study, Fluegge conclusively demonstrated the significance of bacteria-laden droplets sprayed from the nose and mouth during speech. Ordinary conversation can disseminate bacteria 4 to 5 meters from the mouth of the speaker. Staphylococci and pathogenic

Fig. 1. Ephraim McDowell performing the first ovariotomy in 1809. The surgeon and assistants are wearing street clothes. (From A. Schachner: Ephraim McDowell, Father of Ovariotomy, Philadelphia, 1921, J. B. Lippincott Company.)

streptococci were cultured from the oropharyngeal cavity and the dental caries of surgeons working in the Breslau Clinic.

Fluegge realized the implications of these laboratory findings and inspired a number of additional investigations by Hübner[9] in Mikulicz's Clinic. In the operating room, Hübner tested the mask by varying the number of layers of gauze and the distance between the mask and the mouth. He concluded that the ideal mask should consist of a double layer of narrow-meshed hydrophilic gauze (Fig. 6). However, intimate contact between the gauze and the mouth caused the mask to become impregnated with saliva, creating a contaminated reservoir. Hübner proposed, therefore, that a distance should be maintained between the mask and the wearer's mouth. He devised a wire frame which was constructed to allow the upper border to lie above the nostrils and the lower border to cover the under portion of the chin (Fig. 7). The double layer of hydrophilic gauze was to be stretched over this framework. A mask so fashioned could be sterilized repeatedly. After 6 months' trial by the entire surgical staff, this mask was adopted for routine use.

Independently, Paul Berger[1] of France published his views concerning the surgical mask in 1899. He confirmed his suspicion of the relationship between a sudden increase in wound infections and the intraoral abscess of his surgical assistant. Berger developed a mask consisting of 6 layers of rectangular gauze which was permanently attached to the operating-room gown while the upper border was tied around the head by 2 strings. Many contemporary surgeons did not share his enthusiasm for this device. In fact, the renowned Parisian surgeon, Prof. Terrier, made a public statement that he never did, and never would, use such superfluous equipment.[1]

Lord Moynihan was probably the first surgeon in the English-speaking countries to advocate the routine use of a surgical mask. In his book *Abdominal Surgery,* second edition, 1906, he decisively emphasized it.

DeLee,[3] the American obstetrician, pub-

Fig. 2. William T. G. Morton administering the first ether anesthesia, Oct. 14, 1846. The absence of surgical gowns, caps and masks is apparent. (From N. P. Rice: Trials of a Public Benefactor, New York, 1859, Pudney and Russell.)

Fig. 3. Modern operating room attire.

Fig. 4. Halsted at Johns Hopkins Hospital. Note the use of gowns, caps, and rubber gloves but lack of masks. (From W. S. Halsted: The Surgeon, Baltimore, 1930, The Johns Hopkins Press.)

Fig. 5. Johann von Mikulicz-Radecki of Breslau, Germany, first introduced the surgical mask in 1897. (From Mitt. a. d. Grenzgeb. d. Med. u. Chir. 24: 3, 1908.)

lished his observations on facial masking as a safeguard against puerperal infection in 1907. Initially, he used a thick scarf of cheesecloth for a mask but, realizing that this material eventually permitted contamination by saliva, he later advocated the use of an outer layer of adhesive plaster.

In 1919, Weaver[16] recommended that masks be changed once they become wet. This required the changing of masks during long procedures and between operations. He also urged the use of 2 superimposed masks.

Although surgical masks were employed in a large number of the more prominent centers prior to 1920, it was not until that year that the wearing of masks during operative procedures became generally practiced. A few men remained who doubted the efficacy of masking or who found covering the nose and mouth irksome, yet by the late 1920's the importance of surgical masking was taken for granted and efforts had turned to improving the efficiency of the design. Because filtration was used for the blockage of bacteria in the early masks, the first efforts were directed toward testing masks by varying the types of cloth or numbers of layers.

Engelfried and Farrer[4] found that the filtering efficiency of a gauze mask depended upon the denier of the weave. Their ultimate mask consisted of 6 layers of 9 by 10.5 inch gauze, 40 by 44 strands. Starch was found to increase the retention of bacteria in the fabric. With this mask, the bacterial count in the operating field could be reduced by 90 per cent. This 6-layer mask proved to be extremely efficient, but was quite uncomfortable, particularly in warm weather and for those who must wear glasses during operations.

Davis[2] recognized that covering the mouth alone, leaving the nostrils unprotected, would be completely inadequate since the rhino-

pharynx harbors many pathogenic organisms.

In 1930, Irving Walker[13] surveyed the relationship of seasonal epidemics to wound infections. He found an increase in the incidence of wound infections in the spring. Having received 40 different masks from various surgical groups, he tested them bacteriologically and found them all to be unsatisfactory. He proposed a new mask made of 2 layers of gauze with a 6-inch square rubber sheet between, which he considered germ-proof. Prof. Kirschner of Heidelberg, using the same principle, substituted a sheet of cellophane for the rubber between the 2 layers of gauze.[6] Hans Wulff,[17] among others, was enthusiastic about this mask and in 1953 pronounced it an "absolute barrier against droplet infection."

Masks with a cellophane or rubber layer are impenetrable to respiration and therefore deflect the air stream. However, contagious droplets, instead of being exhaled directly into the operative field, are diverted upward and backward. These organisms are expelled into the ambient air, which is stirred by ordinary operating-room traffic, and thus the organisms may gain access to the wound. Cone, using an impervious mask, improved its efficiency by adding a suction apparatus for the removal of expired air.[12]

Filtering devices have been added subsequently to circumvent this hazard. Edward G. Waters[15] designed a mask of plastacele, (a transparent cellulose derivative) incorporating within it replaceable cotton pledgets for filtration.

In the Kiser-Hitchcock[10] mask, a recent innovation, stream deflection is effectively combined with air filtration. Wearer comfort remains a problem, however.

The ideal mask has yet to be developed. None, so far, has succeeded in combining comfort with bacteriologic security. Conversation during operations multiplies infections hazards. "Stumme Operation," or silent operating, as proposed in the early German literature, is not practical, particularly in training centers where the remarks of the teaching surgeon are of incalculable value to the initiate.

Eventually, a comfortable and aseptic device, as envisioned by Mikulicz 60 years ago, may be created for exclusion of germ-laden expired air of the operating room personnel and thereby reduce the ever-present hazard of wound infection. Even

Fig. 6. Surgical mask as proposed by Hübner and used in Mikulicz Clinic in Breslau in 1898. (From W. Hübner.[9])

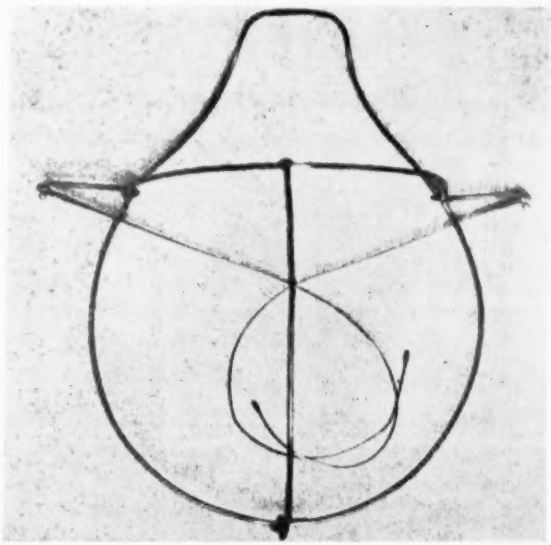

Fig. 7. Wire frame incorporated in the early mask by Hübner.

upon the development of such a device, whether it be in the form of a more perfect mask or some bactericidal medium, other aspects of surgical technique and the care of the wound will continue to be of paramount importance in the prevention of postoperative sepsis.

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